Studies in the synthesis of azasteroids.

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STUDIES IN THE SYNTHESIS OF AZASTEROIDS

Submitted by

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for the degree of Ph.D.

of the University of Bath

1982

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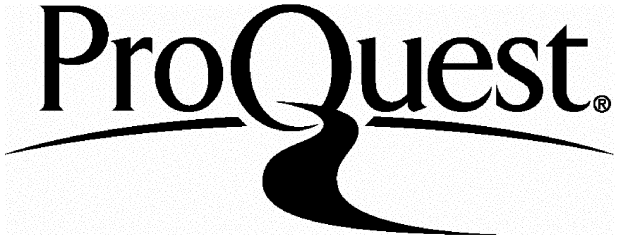

Science is the great antidote to the
poison of enthusiasm and superstition

Anonymous

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SYNOPSIS

This project involved the synthesis of azasteroids with potential GABA (γ-aminobutyric acid)-mimetic activity. Several methods leading to the formation of azasteroids were employed.

The Diels-Alder reaction of isoquinoline-derived dienes with suitable dienophiles furnished several adducts, some of which were tested for biological activity. An unusual double Diels-Alder reaction was observed for some cases i.e. one equivalent of the diene reacted with two equivalents of dienophile to give a "di-adduct". A possible mechanism for this reaction is discussed in Chapter Five.

Many diaza-steroid intermediates were prepared from quinazoline derivatives. These, together with their mechanistic features are discussed in Chapter Six.

The condensation reaction of hydroxy-naphthaldehydes with guanidine afforded benzoquinazolines. Reaction of a benzo[f]quinazoline with chloroacetyl chloride, followed by cyclization resulted in the formation of a tri-azasteroid. These reactions are discussed in Chapter Seven.

The experimental details of the syntheses of 'aza-steroids' and their intermediates, from isoquinoline-, quinazoline-, and naphthalene-derivatives are given in Chapters Nine, Ten and Eleven, respectively.

Results obtained for the biological activity tests of some 'aza-steroids', are discussed in Chapter Eight. Potential future studies are also mentioned in Chapter Eight.

Concise reviews of γ-aminobutyric acid, azasteroids, isoquinolines and quinazolines, pertinent to this project together with background material are given in Part One of the thesis, Chapters One, Two, Three and Four, respectively. A large number of references, necessary for the reviews contained in Part One, are provided.

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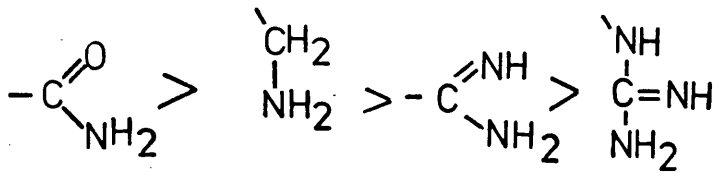
I N T R O D U C T I O N

OBJECTIVES AND RATIONALE

It has been known for some time that the guanidinium moeity[530] plays a decisive role in the blocking of sodium channels[528] and thus preventing the conduction of the nerve impulse. Compounds such as Tetrodotoxin (380) and Saxitoxin (See Chapter 4, p.116) are potent neurotoxins.[529]

The aim of this project was to investigate synthetic methods leading to the formation of steroid-type molecules containing the amidinium or guanidinium groups, with potential GABA-mimetic activity. γ-Aminobutyric acid (GABA)[28] is a central inhibitory neurotransmitter (See Chapter 1). The design of a suitable GABA-mimetic drug must be aimed at obtaining a compound which is less basic than guanidine but more basic than GABA itself. Since GABA is a weaker base than guanidine, it binds relatively weakly to the receptor site and thus is an ideal competitor to calcium ions for the receptor site. Binding affinity of the receptor site is influenced by the basicity of the molecule, i.e. the more basic a molecule, the greater will be its binding force to the receptor site.

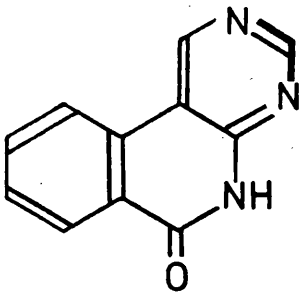


Increasing basicity

Increase in binding strength

The 'steroid' skeleton was employed as a rigid framework, into which were incorporated the appropriate functional groups.

Theoretically, the quinazoline nucleus is an ideal starting point for the synthesis of 'steroidal' structures with potential GABA-mimetic activity. The two nitrogen atoms are arranged in such a manner that they need not be replaced, nor is there a necessity to introduce any further nitrogen atoms during the completion of the synthesis. Synthetic methods were extended to involve the benzo[f]quinazolines as precursors to the desired products. Reports by Caromna[531] and others of syntheses of azasteroid - intermediates from isoquinoline derivatives (for example, see below), prompted the investigation into synthetic methods leading to azasteroids with potential pharmacological activity, from isoquinoline derived intermediates. Several steroid-type compounds were synthesized, some of which were screened for potential biological activity.



PART I

C H A P T E R O N E

REVIEW OF γ-AMINOBUTYRIC ACID

1. γ-Aminobutyric acid as a neurotransmitter

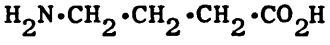
γ-Aminobutyric acid (GABA)(1) is now widely accepted as a principal central nervous system (CNS) inhibitory transmitter. Although the role of GABA in brain function is not fully understood, it is however realised that GABA participates in human motor co-ordination, endocrine function and higher integrative cortical function. Thus, disorders such as Huntington's Chorea, Parkinsonism, epilepsy, spasticity and schizophrenia probably arise due to a malfunction of the GABA system. A large number of drugs, including the barbiturates, benzodiazepines, diphenyl hydantoins and some antipsychotic neuroleptics, have been shown to facilitate GABA neurotransmission.

1.1 History

GABA was identified as an important brain constituent only relatively recently, owing to the fact that it is not found in any significant amount in other tissues.[1,2] Its functional role as an inhibitory transmitter became apparent when Elliott *et al.*[3,4] identified GABA as the active agent in brain extracts which had a unique inhibitory action on crayfish stretch-receptors.[5] The powerful inhibitory effect of GABA on crustacean stretch-receptors and muscle was later shown to be indistinguishable from synaptic inhibition.[6,7] With the further evidence obtained by demonstrating that GABA is selectively released by stimulating inhibitory

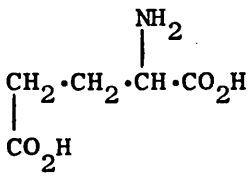
Centrally Acting Putative Neurotransmitters

Amino Acids



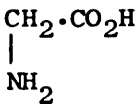
GABA

(1)



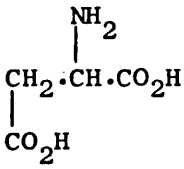
Glutamic Acid

(2)



Glycine

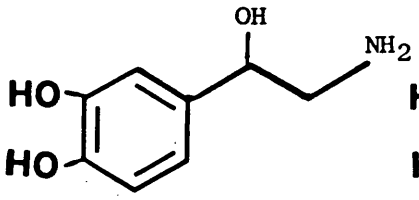
(3)



Aspartic Acid

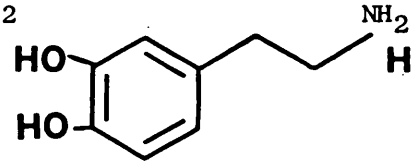
(4)

Others



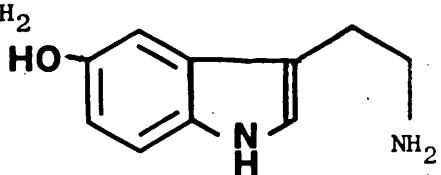
Noradrenaline(NA)

(5)



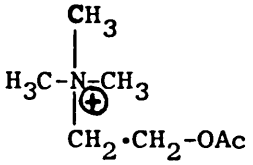
Dopamine(D)

(6)



Serotonin(5-HT)

(7)



Acetylcholine(ACh)

(8)

nerve fibres, it became probable that GABA is an inhibitory transmitter in crustaceans.[8]

Hayashi, in 1955, first noted the inhibitory effect produced by GABA on mammalian cortical neurones. A depressant action was also observed by Purpura et al.[9] and Curtis et al.,[10] but neither group believed that GABA could be responsible for the natural inhibition of central neurones. However, further tests on the cerebral and cerebellar cortex revealed such a powerful inhibitory effect that GABA could not be ignored as a putative inhibitory transmitter.[11] Intracellular recording and studies on membrane resistance,[12] later demonstrated a remarkable similarity between the effects produced by synaptic inhibition and by GABA. In both cases, there was a hyperpolarisation, with a similar reversal level, and a great decrease in membrane resistance, attributable chiefly to an increase in chloride ion permeability.[13]

1.2 Metabolism of GABA

The production of GABA from glutamic acid is mediated by a highly specific enzyme, glutamic decarboxylase (GAD), which requires pyridoxal phosphate as coenzyme, and is inhibited by semicarbazide and hydroxylamine. GAD is also inhibited by chloride ions, so that an increase in the chloride ion content in inhibitory cells, resulting from intense activity, could substantially reduce the rate of production of GABA.

GABA-amino-transferase (GABA-T) is another important enzyme involved. By reversible transamination with α-oxoglutarate, it converts GABA to succinic semialdehyde, which, in the presence of an appropriate dehydrogenase, is oxidised to succinic acid. Succinic acid is required by the tricarboxylic acid (TCA) cycle, and so GABA is conveniently removed by this route (see Scheme 1).

An alternative pathway leading to the production of GABA is *via* the oxidative decarboxylation of arginine resulting in γ-guanidobutyrate which is a precursor of GABA.

Scheme 1

GABA-metabolism in the Brain[15]

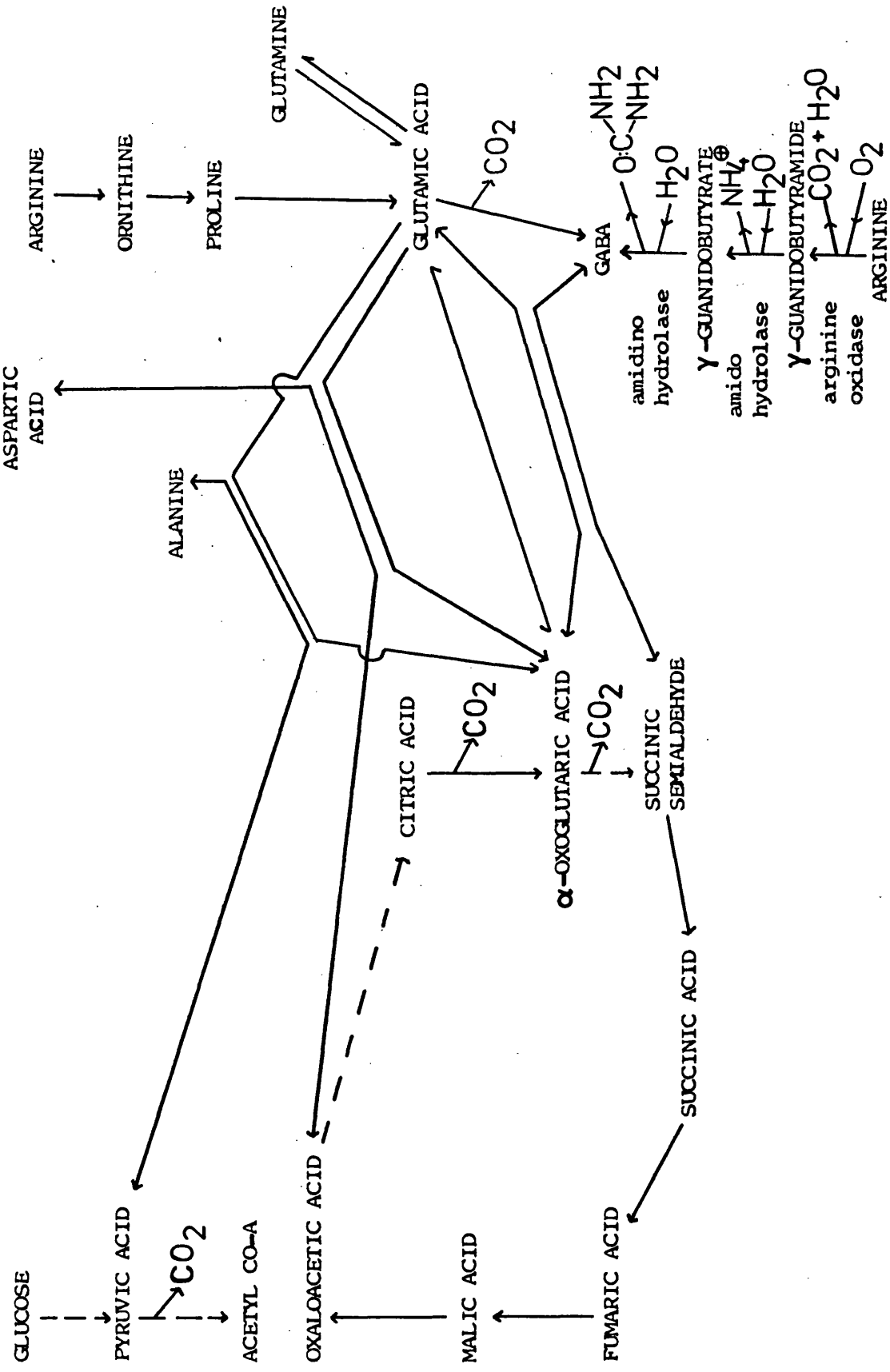
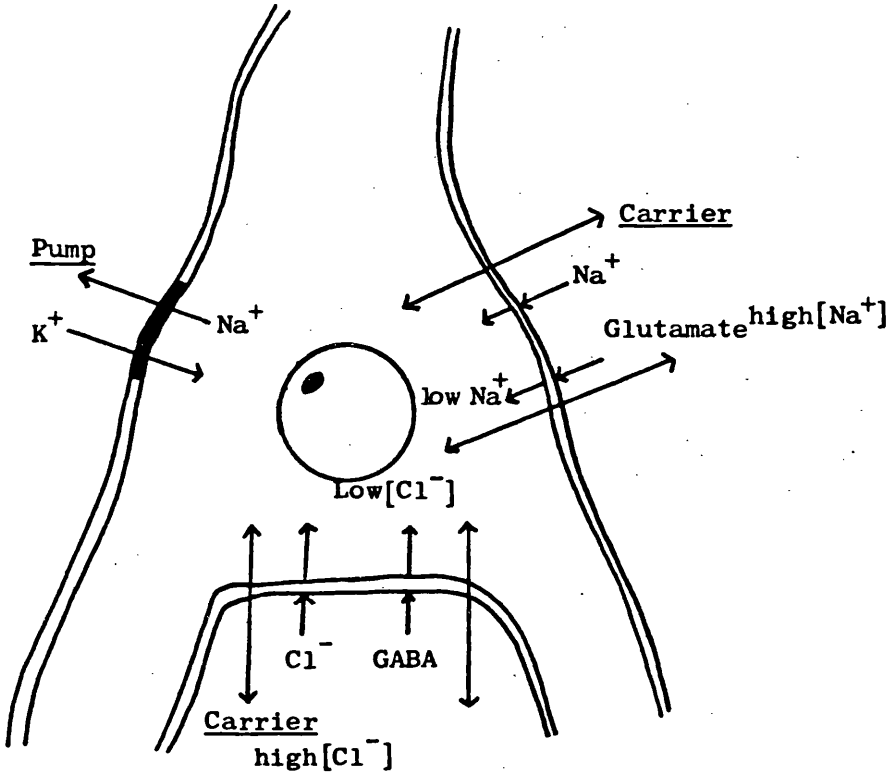
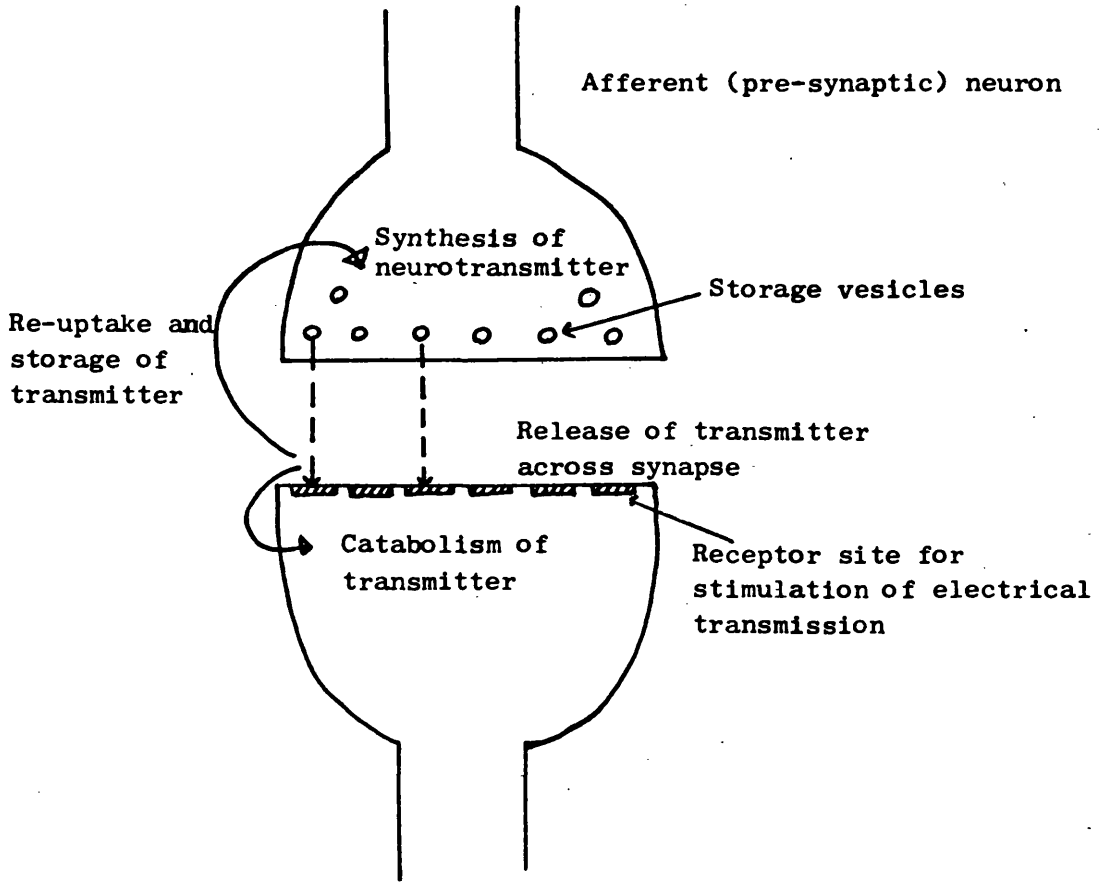


Figure 1



Chemical Transmission in the Central Nervous System



1.3 Structure of GABA

GABA is a flexible molecule. X-ray crystallography indicates that GABA in the solid state, exists in a partially folded conformation,[16] while proton magnetic resonance studies[17] favour extended conformations for GABA in solution. There is also evidence for extended conformations of GABA under *in vivo* conditions.[18] This amino acid exists as a zwitterion at neutral pH and pK values of 4.03 and 10.27 at 35°C.[19]

1.4 Localization of GABA in Brain

GABA occurs in mammals in appreciable amounts only in the CNS, with the highest levels in the substantia nigra and globus pallidus. GABA is too powerful an inhibitor to be freely distributed in the extracellular space of the brain. When GABA is injected inside neurones, it does not alter their excitability,[20] therefore it could be stored within cells. In fact, most of the GABA in the brain is probably actively stored in an intracellular compartment. Fluid left in contact with the surface of the brain contains at most only traces of GABA. Slices of cerebral cortex absorb GABA, even against a very high concentration gradient. This active process requires the expenditure of energy, and is therefore blocked by metabolic inhibitors.

While it is generally accepted that systemically administered GABA does not raise levels in the brain, subcutaneous injection of large doses (60 μmole/g) increases the brain levels in mice.[21]

The concentration of GABA in the brain can be altered by a variety of drugs, many of which inhibit GABA-metabolizing enzymes.

Although GABA itself is not incorporated into protein, it does stimulate protein synthesis in cell free extracts of immature rat brain.

Histochemical methods can be used for the localization of GABA[22] in the brain. Use has also been made of the distribution of radiolabelled thiosemicarbazide as an indicator of GABA metabolism.[23]

1.5 GABA as a Neurotransmitter

Increasing evidence has been obtained to suggest that amino acids are involved in chemical synaptic transmission, by subjecting the amino acids to the criteria established for neurotransmitters such as acetylcholine (ACh) and the catecholamines:-

i) their concentration relative to other regions of the nervous system must be high;

ii) the enzyme(s) involved in their synthesis must show a high activity;

iii) the nerve endings must possess a selective high affinity uptake mechanism.

All those presynaptic characteristics would then diminish or disappear when the terminals degenerate following a lesion of the

afferent neuron or axon. Also, the transmitter substance should be released from the nerve terminals, either through the effect of high K^+ concentration or drugs such as veratridine, or through electrical stimulation.

Evidence for GABA as a neurotransmitter

The evidence for certain amino acids as synaptic transmitters includes information about:-

I the synthesis and storage within presynaptic nerve cells,

II the release from presynaptic terminals,

III the interaction with receptors on the postsynaptic neurones and the consequent transient alterations in ionic permeability of the subsynaptic membrane,

IV the ability of certain substances to antagonise both amino acid- and synaptically-induced postsynaptic effects,

and V the processes associated with the inactivation and removal of amino acids from the synaptic environment.

Experimental difficulties abound in all aspects of these investigations, since lists of criteria for transmitter identification were originally drawn up on the basis of experience regarding the transmitter function of acetylcholine at vertebrate neuromuscular and ganglionic synapses.

1.5.1 I Synthesis and Storage in Presynaptic Terminals

Consideration of GABA as a central transmitter originated from its presence in vertebrate brain tissue,[24] and studies of the

gross distribution of GABA, GAD and GABA-T have been of prime significance in establishing the importance of this amino acid. More specific and detailed information has been provided using microdissection and microanalytical techniques; such investigations providing, for example, a measure of the amounts of GABA and GAD within synaptic terminals.[25] In both the spinal cord and cuneate nucleus depletion of GABA by the administration of agents which inhibit GAD, leads to a reduction of GABA-mediated inhibitions. The convulsant effects produced by these agents may also be related to the reduced amount of GABA available for synaptic release in these and other regions. Cytochemical techniques, including autoradiographical localization of labelled GABA within synaptic terminals after *in vivo* or *in vitro* uptake, are being employed. Also, the immunohistochemical visualization of GAD has been an indicator of synaptic sites of GABA synthesis.

1.5.2 II Synaptic Release of GABA

Owing to the large number of problems involved in demonstrating *in vivo* the synaptic release of any central transmitter, very few studies have shown that impulses in a putative gabergic pathway release GABA.[26] Although a Ca^{2+}-dependent release of GABA can be induced *in vitro* from tissue slices or synaptosomes, by electrical 'stimulation' or increased K^{+} concentration, this release is difficult to relate to that occurring synaptically *in vivo*, except where the degeneration of a pathway does or does

not influence the release in vitro from slices prepared from the relevant region of the CNS.[27]

1.5.3 III Postsynaptic Action of GABA

Microelectrophoretic methods have established two central actions of GABA and close analogues:-

a) hyperpolarization of neurones produced by an increase in membrane permeability to Cl^- (and possibly also K^+) which appears identical to the permeability increase induced at inhibitory synapses, and also by 'glycine-like' amino acids,[28] and

b) depolarization of primary afferent terminals which, although also associated with an increased permeability to Cl^-, is not produced by 'glycine-like' amino acids.[29]

These effects establish a relationship between GABA and post-synaptic (hyperpolarizing) inhibition, and also between GABA and presynaptic inhibition. The former required additional use of specific antagonists of the action of GABA, to exclude the involvement of 'glycine-like' amino acids as transmitters.

Under in vitro conditions, GABA binds in a sodium-independent manner to synaptic membrane fractions of mammalian brain at sites which can be distinguished by substrate specificity from those associated with the sodium-dependent membrane transport of this and related amino acids.

1.5.4 IV Postsynaptic Antagonists of GABA

Since the postsynaptic effects of 'glycine-like' and 'GABA-like' amino acids appear identical, specific antagonists of these two classes of inhibitory amino acid have been required to distinguish glycine- from GABA-mediated synaptic processes.

Inhibitions sensitive to low strychnine concentrations are regarded as being mediated by a 'glycine-like' amino acid; whereas (+)-bicuculline methochloride, (+)-bicuculline and picrotoxin block both the hyperpolarizing effect of 'GABA-like' amino acids on neurones and the depolarization of primary afferent terminals. Thus, GABA can be accepted as the most probable transmitter when a synaptic process can be suppressed or reduced by bicuculline, but is not affected by strychnine.

1.5.5 V Inactivation and Removal of Synaptically Released GABA

In view of the predominantly intracellular location of GABA-metabolizing enzymes, the factors involved in the removal of synaptically released GABA from the extracellular environment appear to be diffusion and carrier-mediated cellular uptake into neurones, terminals and glial cells. There is no evidence to suggest that GABA is inactivated enzymically in the extracellular synaptic environment. Uptake by synaptic terminals could provide a supply of transmitter for re-use. Both low- and high-affinity transport mechanisms have been identified:[30] the former is significant when subsynaptic concentrations of GABA are

relatively high immediately after synaptic release, whereas the latter is most important for maintaining very low extracellular concentrations of the amino acid.

Under *in vitro* conditions a number of compounds inhibit GABA uptake, and the receptor sites differ from those associated with the postsynaptic action of GABA.[31] Also, these substances, particularly (+)-2,4-diaminobutyric acid, (-)-nipecotic acid, guvacine and arecaidine, selectively enhance and prolong the effects of micro-electrophoretic GABA *in vivo*.

An important characteristic of GABA-mediated inhibitions is the enhancement and prolongation by anaesthetics, particularly by the barbiturates which also similarly influence the effect of micro-electrophoretic GABA but not that of glycine.

1.6 Mechanism of GABA Action

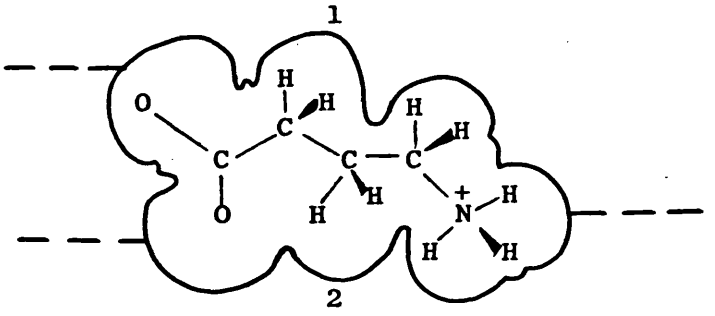
GABA produces an increase in membrane permeability to chloride ions which can be measured as an increase in membrane conductance. It is in this manner that this naturally occurring transmitter can counteract the depolarizing action of excitatory processes, to maintain the polarization of a cell at an equilibrium level near that of its resting value, acting essentially as a chemical voltage clamp. GABA can exert a hyperpolarizing (inhibitory) effect *via* this mechanism. However, when the intracellular chloride ion concentration is high, GABA can produce a decrease in membrane potential (depolarization), a mechanism involved in presynaptic inhibition (see Figure 1).

Much evidence suggests that GABA-anionophore complexes exist in some excitable membranes which function in such a manner that, when GABA or a suitable agonist attaches to the GABA recognition site, anion channels are opened for a period during which GABA is attached to such sites. Recent work suggests that convulsants such as picrotoxin, bicuculline, penicillin and pentylenetetrazole, and the anticonvulsants such as diphenylhydantoin, diazepam and phenobarbitone, decrease or increase, respectively, the efficacy of GABA synapses.[32,33]

GABA acts on its receptor in the extended form[31,34] (see Figure 2). The atoms which protrude from the surface and might be the first ones to hit a membrane surface that would be approached by the faces of the molecules, are shaded. This is the surface of GABA, a receptor site would recognise. Figure 3 shows a comparison of "binding site" faces for GABA and two of its agonists - muscimol and imidazoleacetic acid.

Figure 2

GABA



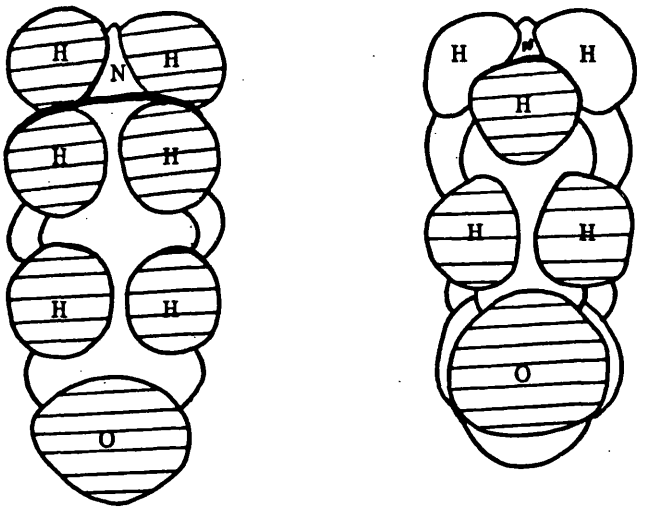


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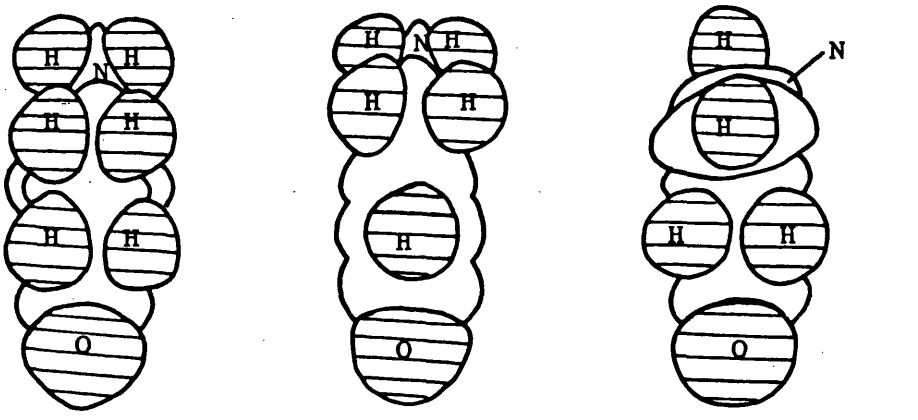
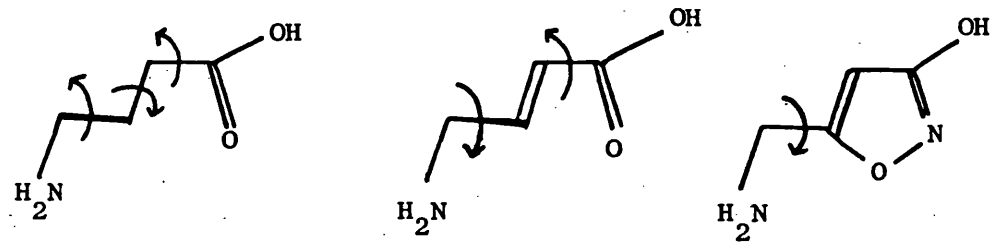
Figure 3



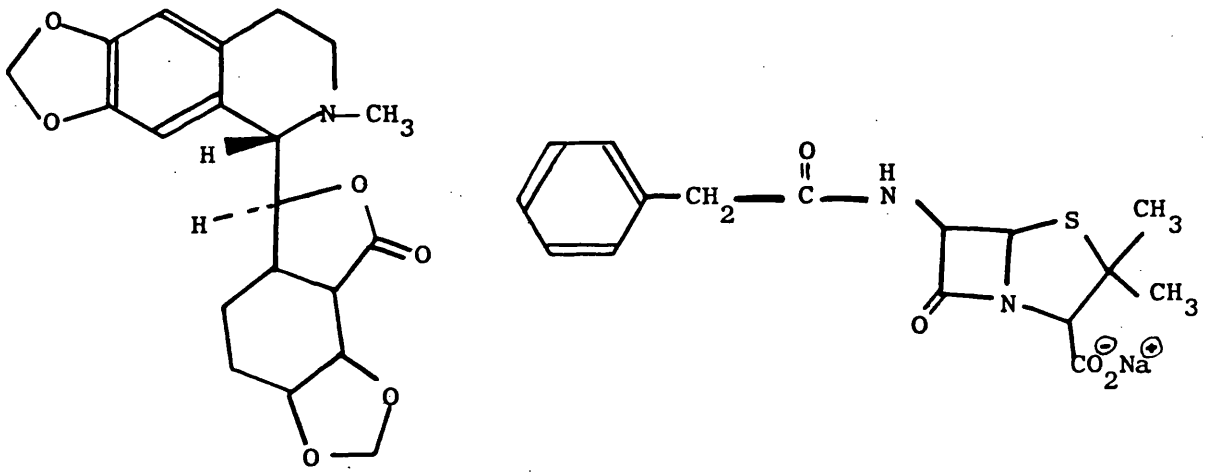
GABA Muscimol Imidazoleacetic acid

Figure 4

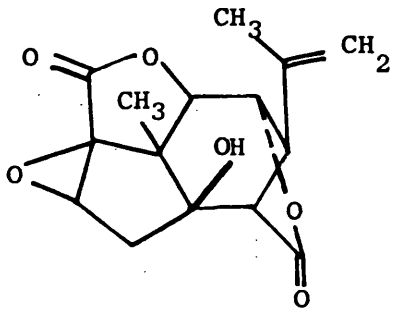


GABA trans-ACA Muscimol

Figure 5



Bicuculline Benzyl Penicillin



Picrotoxin

1.7 GABA Agonists

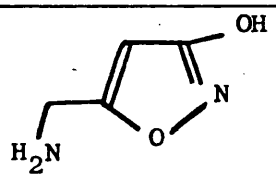
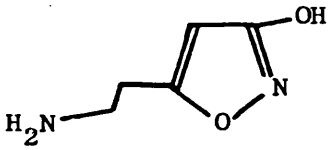
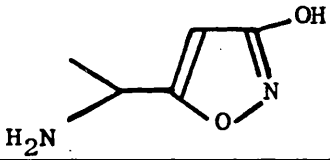
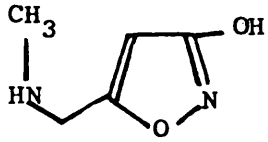
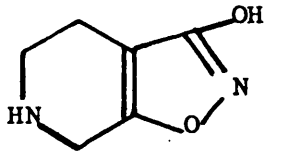
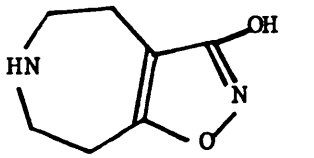
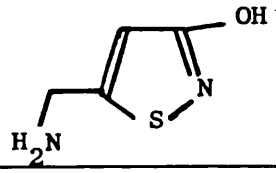
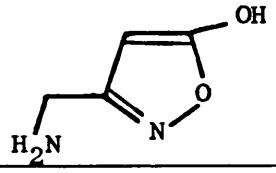
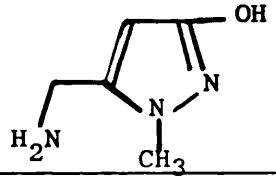
GABA appears to be involved in the development of certain neurological and psychiatric disorders such as Huntington's Chorea, Parkinson's disease and schizophrenia. These diseases may be treated by pharmacological manipulation of the GABA mediated synaptic mechanisms by employing agents which specifically interact with or increase neurotransmitter function.

The 'active conformations' of GABA with respect to its pre- and post-synaptic receptors can be elucidated *via* structure-activity studies on compounds of semirigid structure which mimic the activity of GABA on its receptors. Such compounds are of great pharmacological interest and may be model compounds for the development of therapeutically useful GABA agonists. Muscimol (5-amino-methyl-3-isoxazolol)[36,37a] and trans-ACA (trans-4-amino-crotonic acid)[38] are powerful GABA agonists with respect to bicuculline-sensitive GABA receptors. Both muscimol and trans-ACA have a lower conformational mobility than GABA, as shown by the rotational freedom round carbon-carbon single bonds (see Figure 4). Whereas trans-ACA is a potent inhibitor of GABA uptake[39] and also a substrate for GABA-T [40], muscimol is an almost specific GABA agonist, being only a weak inhibitor of GABA uptake.[41]

Using microelectrophoretic techniques, a series of isoxazole derivatives related to muscimol have been tested as GABA agonists on single neurones by Krogsgaard-Larsen *et al.*,[42,44] using the procedure described by Enna and Snyder.[43] (Tables 1 and 2 show the potency of muscimol analogues and other compounds as inhibitors of ^{3}H-GABA binding,

Table 1[31]

Some Muscimol Analogues as GABA Agonists

Isoxazole derivative	Formula	% Inhibition	Rel. Potency	pK Values
	GABA		(+)	4.0;10.7
Muscimol		103±4	(+)	4.8; 8.4
		91±1	(+)	5.1; 9.5
		89±1	(+)	4.7; 8.5
N-methyl muscimol		59±1	not tested	-
THIP		97±1	(-)(+)	4.4; 8.5
		39±4	(0)	4.8; 9.2
Thiomuscimol		114±2	(+)	6.1; 8.9
Isomuscimol		42±1	(0)	2.6; 9.0
1-Methylaza-muscimol		26±1	not tested	8.0;10.0

stated as % inhibition when tested at concentrations of 10^{-4}M; and as depressants of neuronal firing compared to that of GABA.)

It has recently been shown that unilateral injection of GABA into the caudal part of substantia nigra, induces contralateral turning in rats. This effect can be mimicked by small amounts of three GABA-ergic drugs:- muscimol, baclofen, and imidazole-acetic acid[35] (see Table 4).

1.8 GABA Inhibitors

There are four main types of GABA inhibitors:-

(i) Inhibitors of GABA synthesis;
(ii) " " " degradation;
(iii) " " " uptake;
(iv) " " " release.

1.8.1 Inhibitors of GABA Synthesis

The main metabolic pathway of GABA synthesis involves the decarboxylation of L-glutamate catalysed by glutamate decarboxylase (GAD), a pyridoxal phosphate-dependent enzyme which is localized in nerve terminals. 3-Mercaptopropionic acid, a potent competitive inhibitor[45] of GAD, produces convulsions due to a decreased GAD activity and reduced GABA levels in rats.[46] Many endogenous factors can inhibit GAD. Zinc ions are potent inhibitors; since zinc is one of the richest divalent metals in

Table 2[31]

Isoguvacine and Related Amino Acids as GABA Agonists

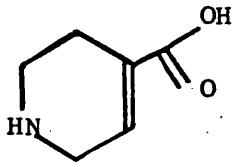
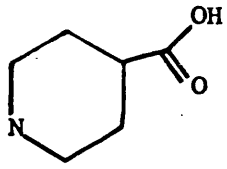
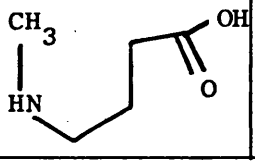
Compound	Formula	% Inhibition	Rel. Potency
Isoguvacine		91±6	(+)
Piperidine-4-carboxylic acid		87±3	(+)
N-Methyl GABA		18±1	(O)

Table 3[31]

Cyclic Amino Acids as Inhibitors of GABA Uptake

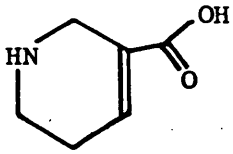
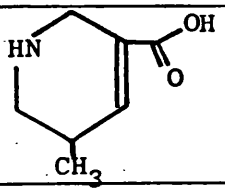
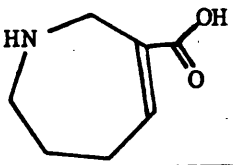
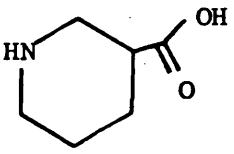
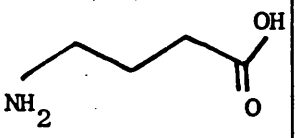
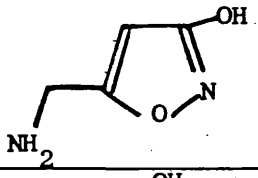
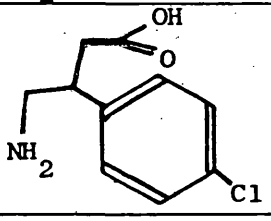
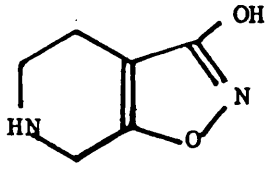
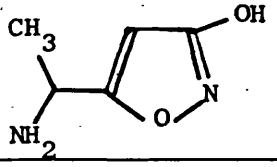
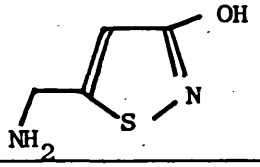
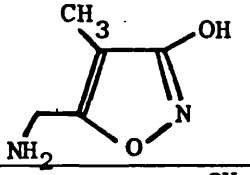
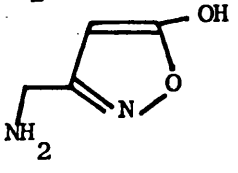
Compound	Formula	% Inhibition	Potentiation of GABA
Guvacine		98±1	(+)
(±)-5-Methyl guvacine		46±1	not tested
2,5,6,7-Tetrahydro-1H-azepine-3-carboxylic acid		23±2	not tested
(±)-Nipecotic acid		-	(+)

Table 4

Turning-behaviour Produced by Administration of GABA Agonists

Compound	Formula	Minimum Dose (µg)	Turning Response	
			Turns/min. (max.frequency)	Duration of action(mins.)
GABA		100	4-28	4-30
Muscimol		0.03	12-30	60-120
Baclofen		0.1	12-31	>150
THIP		0.3	8-18	30-85
5'-Methyl-muscimol		1.0	5-30	30-90
Thiomuscimol		3.0	6-15	6-7
4-Methyl-muscimol		15	15-40	40-80
Isomuscimol		85	0	0

brain, it may be involved in the regulation of cerebral excitability. Sulfhydryl agents such as glutathione and cysteine could also be important in modulating GAD activity. Folic acid is a weak competitive inhibitor of GAD and this may be associated with some forms of epilepsy where folate levels increase. Huntington's Chorea is associated with a decrease in GAD activity in the basal ganglia.[47] Many structural analogues of glutamate inhibit GAD.[48]

1.8.2 Inhibitors of GABA Degradation

GABA is metabolised to succinate by transamination to succinic semialdehyde catalysed by GABA-transaminase (GABA-T), and subsequent oxidation catalysed by succinic semialdehyde dehydrogenase (SSAD). Selective inhibition of either enzyme generally leads to increased levels of GABA accompanied by an anticonvulsant action. Aminooxyacetic acid (AOAA) is a potent competitive inhibitor of GABA-T, and is one of the most widely used agents for increasing the levels of GABA in brain.[49,50] AOAA is a carbonyl-trapping agent which is a quite potent competitive inhibitor of GAD.[45,70] Ethanolamine-o-sulphate (EOS) is an active-site directed irreversible inhibitor of GABA-T.[51] Like AOAA, EOS is a weak inhibitor of GABA uptake,[52] but unlike AOAA it does not inhibit GAD. Sodium Di-n-Propylacetate (DPA, sodium valproate) is a competitive inhibitor of GABA-T[53] but has a more potent action on SSAD.[54] DPA has been used clinically in the treatment of epilepsy. Systemic administration of DPA protects against seizures and increases brain levels of GABA.[53]

Consideration of the mechanism of GABA-T action, led to the synthesis of γ-acetylenic GABA (GAG, 4-aminohex-5-ynoic acid) as a

catalytic inhibitor of GABA-T. GAG binds to the active-site of GABA-T and causes a subsequent time-dependent irreversible inhibition. The active-site catalytic inhibitor of GABA-T was discovered in a culture filtrate of streptomyces toyocaemis and was characterised as (-)-5-aminocyclohexa-1,3-diene-1-carboxylic acid (Gabaculline).[56] Gabaculline is a weak inhibitor of GAD and a moderately potent inhibitor of GABA uptake.

1.8.3 Inhibitors of GABA Uptake

GABA is transported by structurally specific sodium-dependent uptake systems. Autoradiographic studies show that GABA is taken up mainly by nerve terminals and glial cells with L-2,4-diamino-butyric acid and β-alanine,[64] being relatively selective substrates for the neuronal and glial uptake systems respectively, in the cerebral cortex and cerebellum.[57] The neurotoxic amino acid, L-2,4-diaminobutyric acid (DABA), found in various species of Lathyrus and Vicia, is a substrate-competitive inhibitor of the neuronal uptake of GABA.[57] DABA has a weak depressant action on the firing of neurons and potentiates the action of electrophoretically administered GABA on these neurons.[58] D-DABA is much less potent that L-DABA as an inhibitor of sodium-dependent GABA uptake, but is equipotent as a weak inhibitor of sodium-independent binding of GABA to synaptic membranes.[59]

Nipecotic acid, like DABA, is a substrate-competitive inhibitor of the neuronal uptake of GABA.[60,61] Arecaidine and Guvacine, structurally related to nipecotic acid, are also inhibitors of the

neuronal uptake of GABA.[62] The conformationally restricted analogue of GABA, cis-3-aminocyclohexanecarboxylic acid is also a competitive inhibitor of GABA uptake, but is more selective for neuronal compared to glial uptake of GABA than either DABA or nipecotic acid.[63]

A number of centrally active drugs including butyrophenones,[73] phenothiazines,[65] and benzodiazepines[66] inhibit GABA uptake *in vitro*. Various drugs inhibit GABA uptake in a relatively non-specific manner, including p-chloromercuriphenylsulphonate, chloropromazine, (imipramine), (haloperidol), dibutyryl cyclic AMP and the protoveratrines.[69]

1.8.4 Inhibitors of GABA Release

Many drugs act on the synaptic release of GABA. Imipramine,[71,72] haloperidol, chlorpromazine, and diazepam, inhibit the calcium-stimulated release of radioactive GABA from synaptosomes,[66] while pentobarbitone inhibits this release of GABA at the level of the 'late' calcium ionophores.[67]

In both the spinal cord and cerebellum, tetanus toxin appears to block the synaptic release of GABA.[68]

1.9 GABA Antagonists

Dating from 1970, a variety of substances have been shown to antagonize the postsynaptic action of GABA and to reduce certain inhibitions in all areas of the CNS. Membrane binding studies

suggest that some of these substances, e.g. bicuculline, compete with GABA for postsynaptic receptors,[74] while others, e.g. picrotoxin, may interfere with GABA-activated ionophores.[75]

Three series of compounds antagonise the postsynaptic effects of GABA:-

(i) Bicuculline and related compounds;

(ii) Picrotoxin and related compounds;

(iii) Penicillins, e.g. Benzyl penicillin (see Figure 5).

1.9.1 Bicuculline, a convulsant phthalide isoquinoline alkaloid[76] is a relatively specific GABA antagonist.[37] The structurally related compounds corlumine and bicucine methyl ester are similar in potency to bicuculline as convulsants and as GABA antagonists.[77] Quaternisation of the heterocyclic nitrogen atom in bicuculline produces more active compounds, for example N-methyl bicuculline.[78] Bicuculline methiodide is a more powerful convulsant than bicuculline hydrochloride.[78] Bicuculline methochloride,[77] which is about 100 times more soluble in water than bicuculline hydrochloride, and is more active electrophoretically as a selective GABA antagonist, is less effective than bicuculline when administered systemically, owing to its quaternary structure.

1.9.2 Picrotoxin is an equimolar mixture of picrotoxinin and picrotin, the former being about 50 times more active than the latter as a convulsant.[79,80] Picrotoxin reversibly, but not consistently, antagonizes the action of GABA in many areas of the CNS. Picrotoxin does not influence the binding of GABA to synaptic membranes. With respect to crayfish muscle, it appears that picrotoxin acts on the membrane molecule(s) responsible for controlling the GABA-induced chloride flux, the GABA-ionophores, or on the link between receptors and ionophores.[75]

1.9.3 Benzyl Penicillin[81] is a specific but less effective GABA antagonist than bicuculline. Recent studies on crab neuromuscular junction indicate that benzylpenicillin antagonises GABA-induced chloride conductance increases by a weaker competitive inhibition, which may be receptor antagonism, and a more powerful non-competitive inhibition, which may be ionophore blockade.[82]

1.9.4 Other GABA Antagonists include bicyclic phosphates;[83] tubocurarine and nicotine;[84,85] certain caprolactam derivatives[86]; and naloxone.[87]

1.10 Conclusion

GABA is considered to be the major central inhibitory transmitter on the basis of its involvement at virtually all levels of the mammalian neuroaxis.

The most fully documented case for an amino acid transmitter, and indeed for any central transmitter, is that for GABA, released at terminals of Purkinje cell axons to inhibit Deiters' neurones. Evidence is available to confirm that GABA is an inhibitory transmitter in the cerebral, cerebellar, and hippocampal cortices, released by basket-type cells. GABA also appears to be an inhibitory transmitter in the substantia nigra (which contains the highest levels of this amino acid in the brain), in the retina, olfactory lobe, thalamic relay nuclei, dorsal column nuclei and the spinal cord.

Defects of GABA-mediated synaptic transmission underlie many neurological disorders, such as epilepsy, various extrapyramidal syndromes, and psychiatric disturbances. The use of agents, based on knowledge of the synthesis, action and inactivation of GABA, may be clinically beneficial. Although the actions of substances found to be therapeutically effective, such as the benzodiazepines, barbiturates, butyrophenones and some anticonvulsants, are probably related to gabergic synapses, the development of these has not yet been based on an understanding of the molecular aspects of gabergic transmission. It will thus be important to study the different types of GABA receptors in various regions of the human brain, both normal and diseased. Major problems which limit such a chemotherapeutic approach are

blood-brain barriers to agents acting at GABA receptors and the clinically undesirable modification of gabergic transmission at relatively normal synapses by an agent required to act specifically with a particular defective pathway.

REVIEW OF AZASTEROIDS

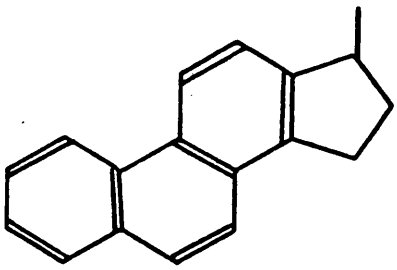
2. Azasteroids

2.1 Introduction to steroids

2.1.1 History

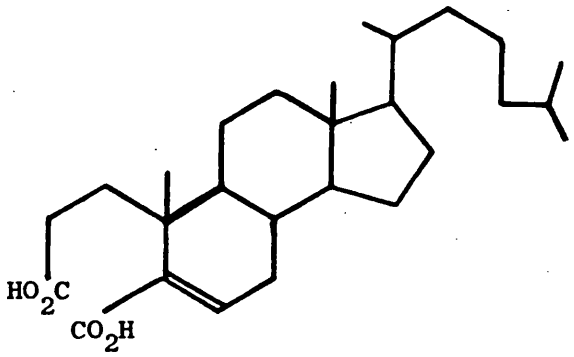
A white, crystalline, unsaponifiable substance was isolated from human gall-stones, about 200 years ago, which in 1816 was named cholestérine (Greek: Chole-bile; Stereos-solid). In 1859 when the presence of a secondary alcohol was detected, the more descriptive name - cholesterol became generally accepted. Preparation of the dibromide of the substance indicated the presence of a double bond. In 1888, the empirical formula for cholesterol was confirmed as $C_{27}H_{46}O$.

Diels'[88] discovery that cholesterol was converted to the hydrocarbon(9A) by selenium dehydrogenation, and, X-ray crystallographic measurements by Bernal[89] lead to the elucidation of the correct structure (10) in 1932 by Rosenheim and King,[90,91] and, Windaus, Wieland and Dane.[92,93]



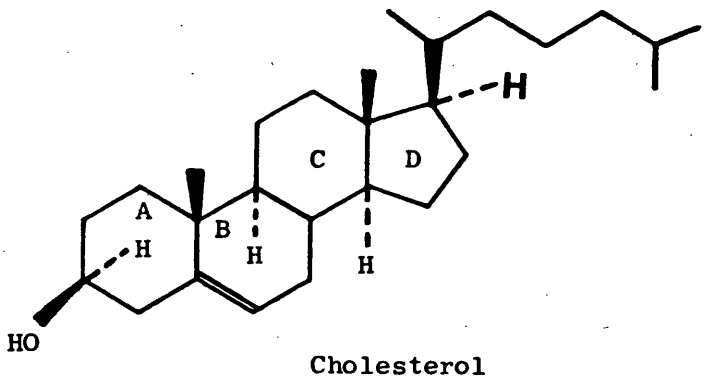
Diels' Hydrocarbon

(9A)



Diels' Acid

(9B)



Cholesterol

(10)

2.1.2 Occurrence

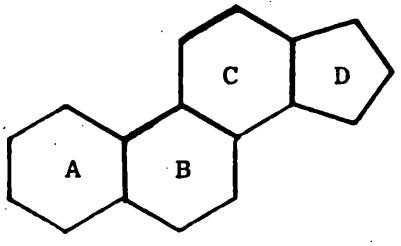
Substances of considerable medicinal importance are found amongst the steroids, occurring naturally in both plants and animals. These include the sex hormones, such as oestrone(12), androsterone(13), and progesterone(14); the adrenocortical hormones such as cortisone(15); the antirachitic vitamin, vitamin D_2(16); and, the cardiac glycosides (sugar derivatives of steroids) such as digitoxigenin(17).

The plant steroids[96] can be divided into four major groups:- sterols, sapogenins, cardiac aglycones,[94] and, alkaloids.[95] The glycoside, solanine, of the alkaloid solanidine(18) occurs in potato sprouts. The important sapogenin, diosgenin(19) isolated[97] from Dioscorea, and cholesterol(10) have been useful starting materials for the synthesis of cortical and sex hormones. More recently, Hardman et al.[152] have extracted diosgenin from Fenugreek.

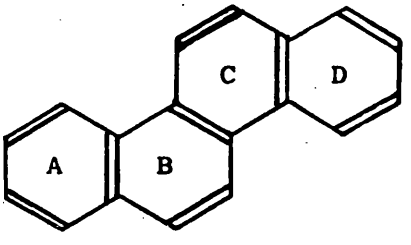
Insect hormones such as ecdysone(20) are also based on the steroidal structure. The bile-acids occurring as conjugates with amino acids, for example, glycocholic acid ($R{\cdot}CONH{\cdot}CH_2{\cdot}CO_2H$) contain steroid fragments such as cholic acid(21) linked as the amide to glycine.

2.1.3 Structure

The steroids are a group of substances possessing a tetracyclic backbone(11A), containing four or more fused rings as in the chrysene (11B) ring system. One or more of the rings A, B, C, and D may be larger or smaller than 6-membered, but usually, rings A, B, and C are 6-membered, and ring D is 5-membered. Heteroatoms may appear anywhere in the ring system, but many naturally occurring steroids are carbocyclic.

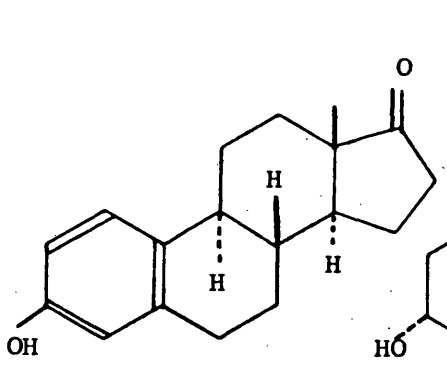


(11A)

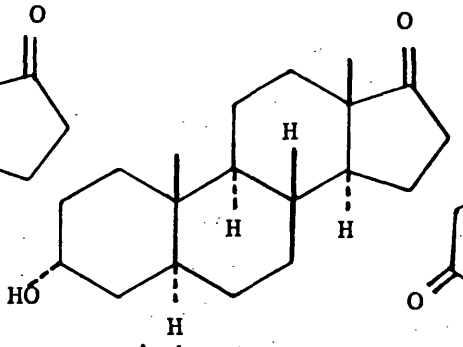


Chrysene

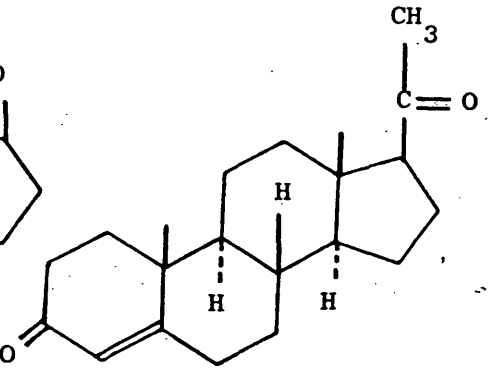
(11B)



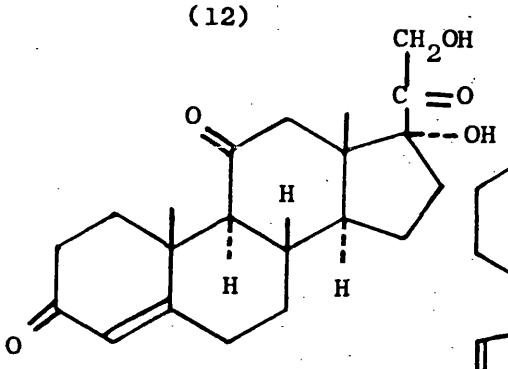
Oestrone
(12)



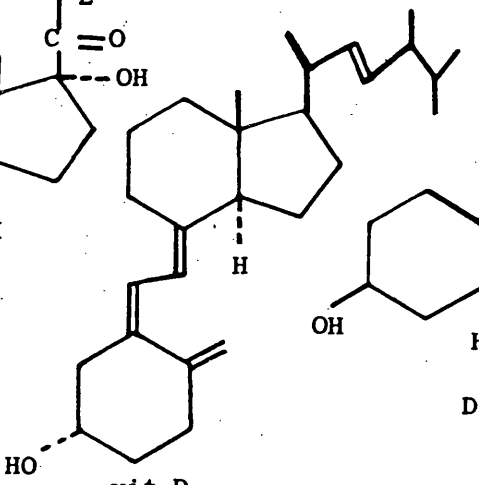
Androsterone
(13)



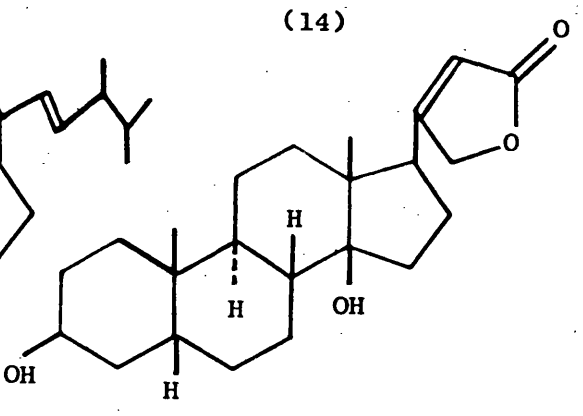
Progesterone
(14)



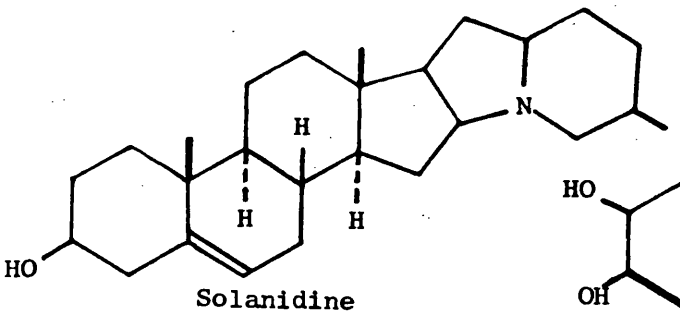
Cortisone
(15)



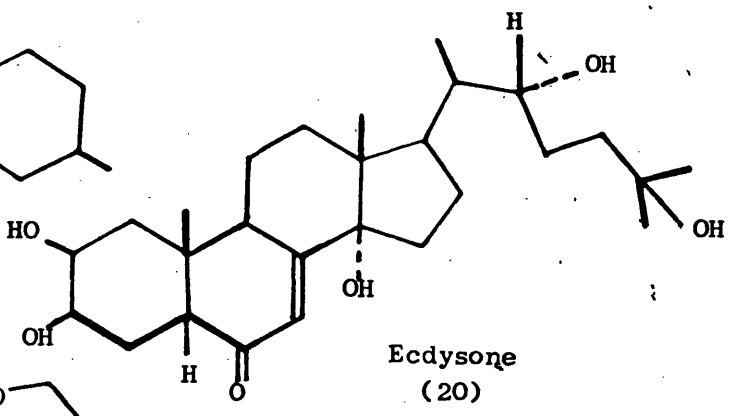
vit.D_2
(16)



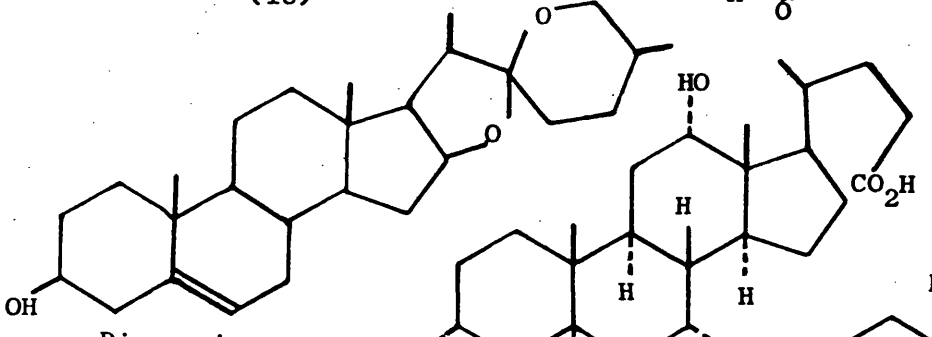
Digitoxigenin
(17)



Solanidine
(18)

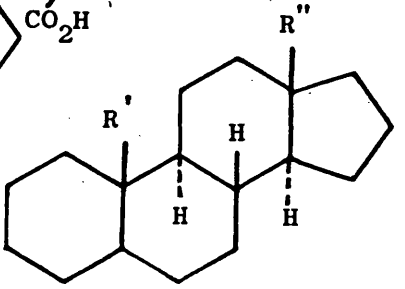


Ecdysone
(20)



Diosgenin
(19)

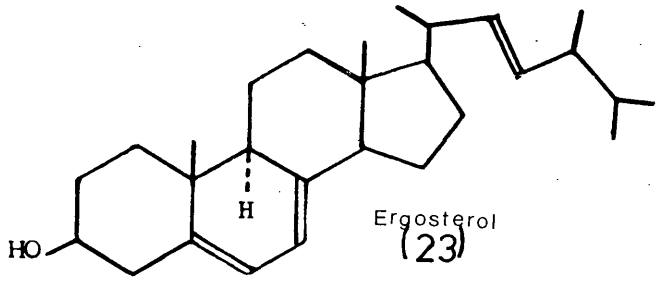
Cholic Acid(21)



(22) Gonane $R'=R''=H$

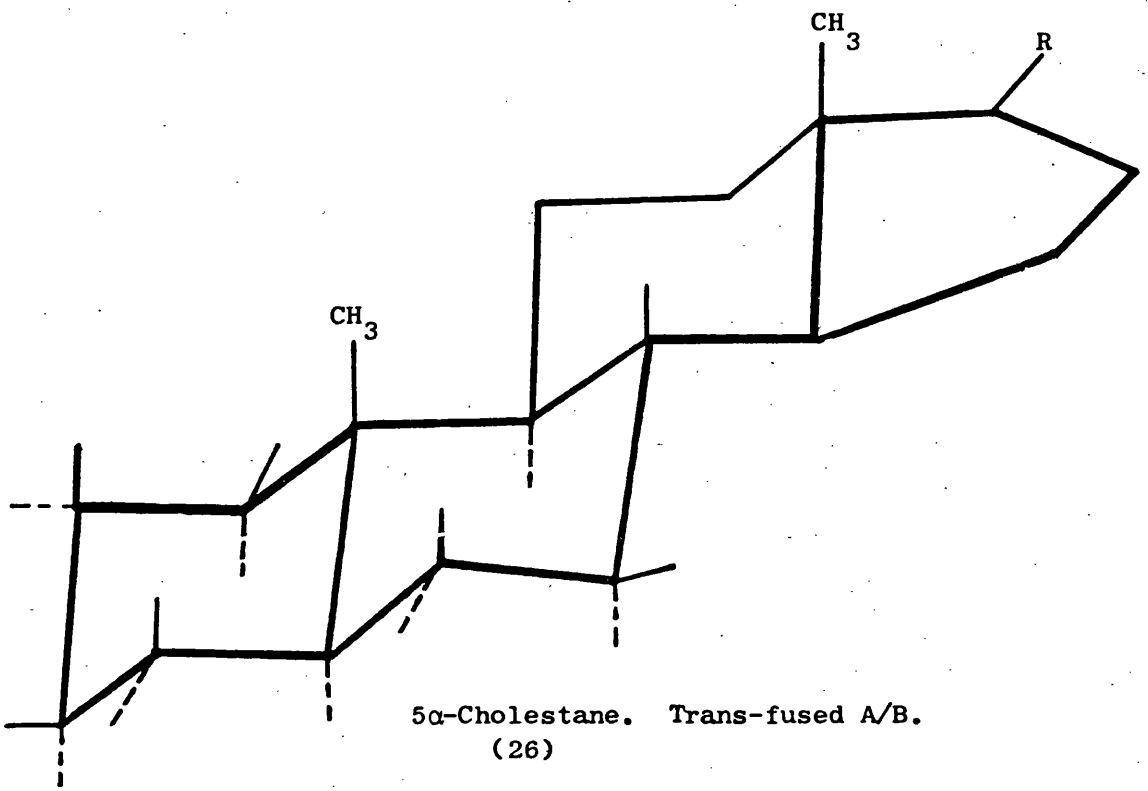
(24) Oestrane $R'=H$; $R''=CH_3$

(25) Androstane $R'=R''=CH_3$

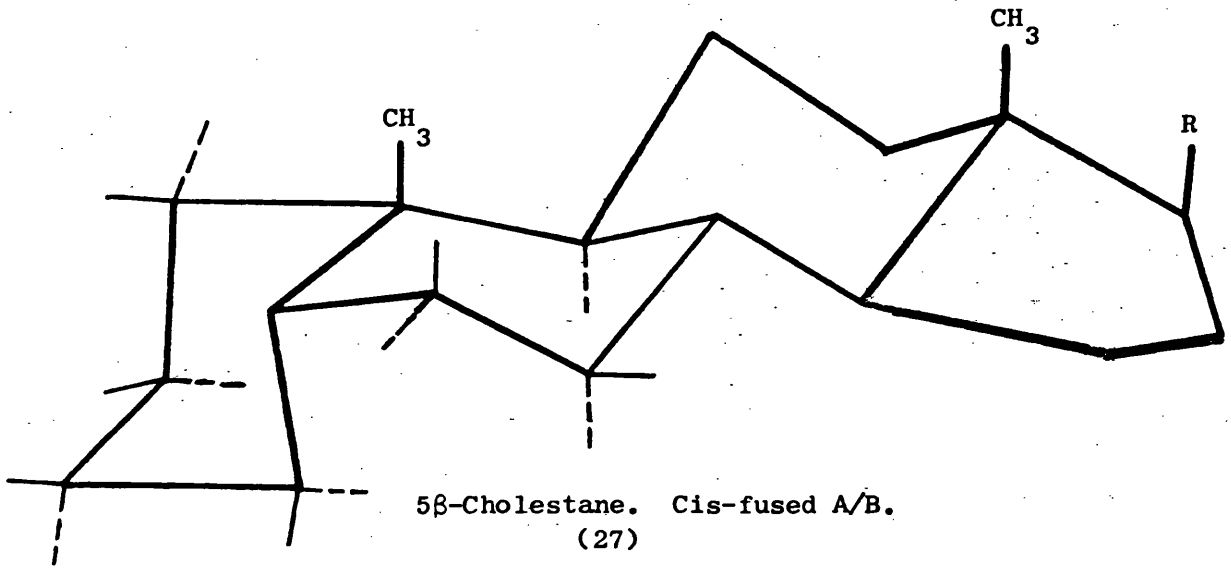


Ergosterol
(23)

The hydrocarbon lacking both methyl groups and a side-chain is named Gonane(22), whilst the saturated hydrocarbon which lacks a methyl group at C-10 and the side-chain at C-17 is named oestrane(24).



5α-Cholestane. Trans-fused A/B.
(26)



5β-Cholestane. Cis-fused A/B.
(27)

The two naturally occurring A/B ring fusions are:-

(a) 'Cis' fusion of the bile-acids, for example cholic acid(21); and

(b) 'Trans' fusion of for example androsterone(13).

(In older texts, the term 'coprostane' is often used to describe the

cis-fusion of 5β-cholestane. Trans-fusion is indicated by the term 'cholestane'.) See structures (26) and (27).

Unfortunately, in a thesis of this type, much of the earlier work on naturally occurring steroids (their isolation, biosynthesis, and total synthesis) has to be omitted. However, for a thorough investigation of the subject the reader is referred to the excellent texts by Fieser,[98] Djerassi,[99] Shoppee,[100] and Akhrem and Titov.[101]

2.1.4 Biosynthesis of steroids

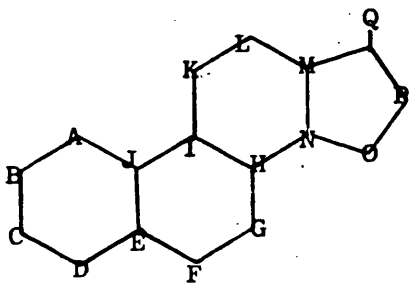
Although a great deal of work has been done in this field to elucidate the biosynthetic pathways of the various naturally occurring steroids in plants and animals, only one pathway will be discussed here in order to show the reader the practical applications of this type of study. Modification of the natural hormones has lead to the production of many drugs which include the oral contraceptives and the anabolic steroids.

2.1.4.1 Biosynthesis of the Sex Hormones

The sex hormones are synthesised in the body from cholesterol(10), which is readily converted to the hormones in a stepwise manner as shown in Scheme 2.

2.2 Synthetic methods leading to the formation of azasteroids

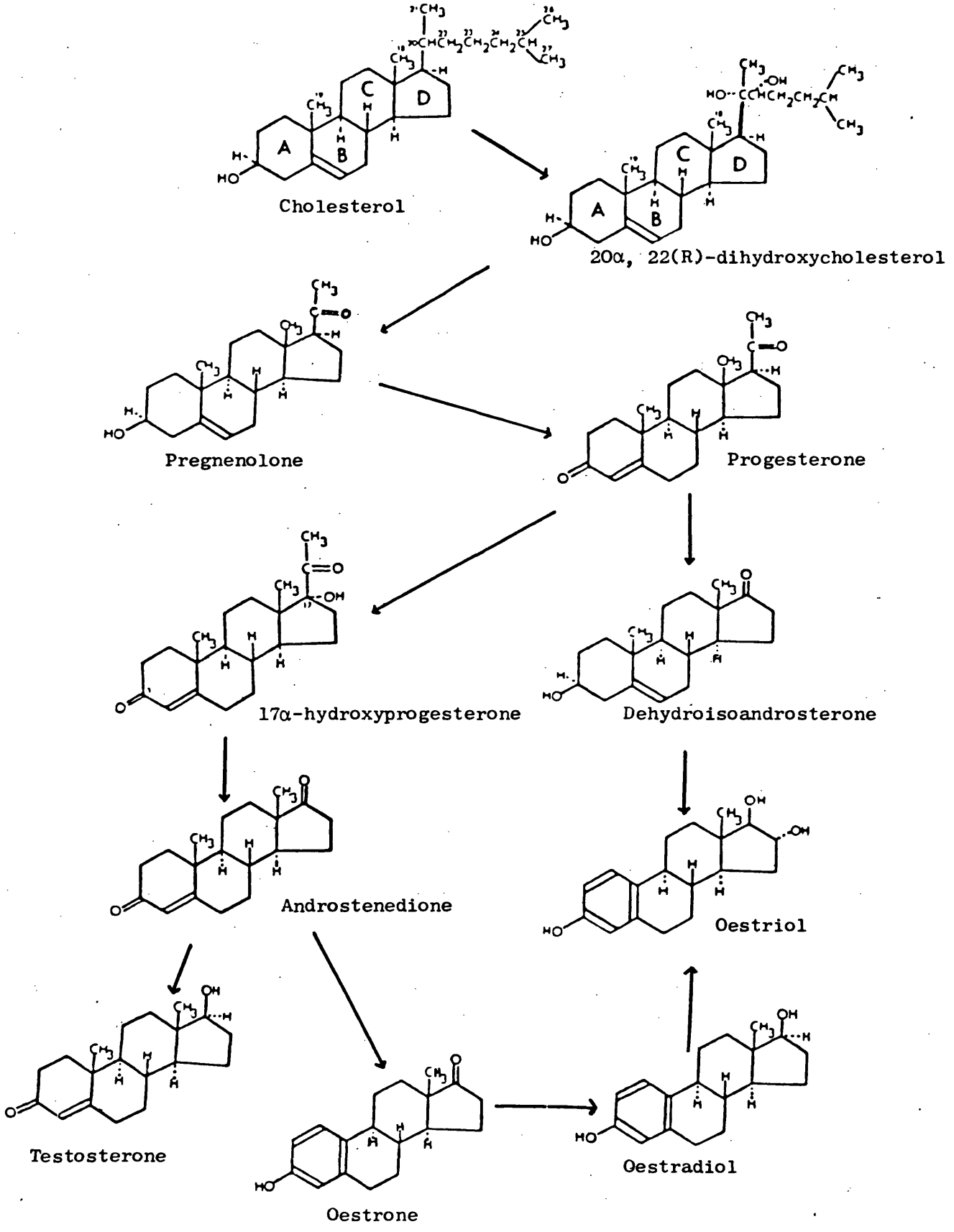
Over the last 20 years, synthetic methods resulting in the formation of a great number of heterosteroidal structures have been reported. If one considers the basic steroid skeleton (28), then theoretically it is possible to synthesise an infinite variety of heterosteroids (where A ⟶ Q is C, N, O, or S.)



(28)

Scheme 2 [153]

Biosynthesis of progesterone, testosterone(androgen) and oestrone(oestrogen) from cholesterol, in man.



The main objective in these types of syntheses is to obtain compounds with enhanced pharmacological activities. However, a great deal of research in this field has provided invaluable information concerning novel synthetic routes and reaction mechanisms as applied to organic chemistry, and has not been of purely academic interest.

The preparation of azasteroids embraces two distinct approaches:-

(i) modification of an existing steroid nucleus either by processes involving ring cleavage, nitrogen insertion and ring closure, or else by application of the Schmidt reaction to an appropriate ketone or of the Beckmann rearrangement of the derived oxime; or

(ii) total synthesis procedures starting with the aza analogues of the precursors of the steroidal skeleton.

Total synthesis represents a difficult task since the steroid molecule contains numerous asymmetric centres. Even in the unsubstituted hydrocarbon gonane(22), there are six asymmetric centres (C-5, 8, 9, 10, 13 and 14) which give rise to 64 isomers. Cholesterol(10) with 8 such centres can have up to 256 stereoisomers.

Azasteroids are compounds in which nitrogen forms an integral part of the steroid nucleus, with or without alteration of ring size, and compounds in which nitrogen appears in one or more side-chain

2.2.1 Naturally occurring azasteroids

(Also see Chapter 3, p.84 , isoquinoline alkaloids.)

2.2.1.1

Among the naturally occurring heterosteroids,[98,104] the more prominent are the extranuclear azasteroids. These include alkaloids present in Solanum, Veratrum, Holarrhena, and Buxus.

The Solanum alkaloids can be divided into two classes:-

(i) the nitrogen analogues of sapogenins, e.g. solasodine(29) and tomatidine(30). Solasodine is similar in structure to diosgenin (19), except -NH is substituted for O in ring F.

(ii) steroids containing a condensed ring system and tertiary nitrogen, e.g. solanidine(31) and demissidine(32). Solanidine was first isolated from the toxic leaves of the black nightshade (S. nigrum). The alkamines - rubijervine (12α-hydroxy-solanidine) and isorubijervine (18-hydroxysolanidine) have been isolated from the rhizomes of Veratrum album.

Large doses of some Solanum alkaloids in animal tests produce parenchymatous nephritis and haemoglobinuria, followed by nervous paralysis and cardiac arrest.

Alkaloids such as veratramine(33) and jervine(34), extracted from the Veratrum plants are not regarded as classical steroids, since they contain a 5-membered C ring and a 6-membered D ring. Several alkaloid esters of germine(35) have been found in the rhizomes of V. album and V. viride.

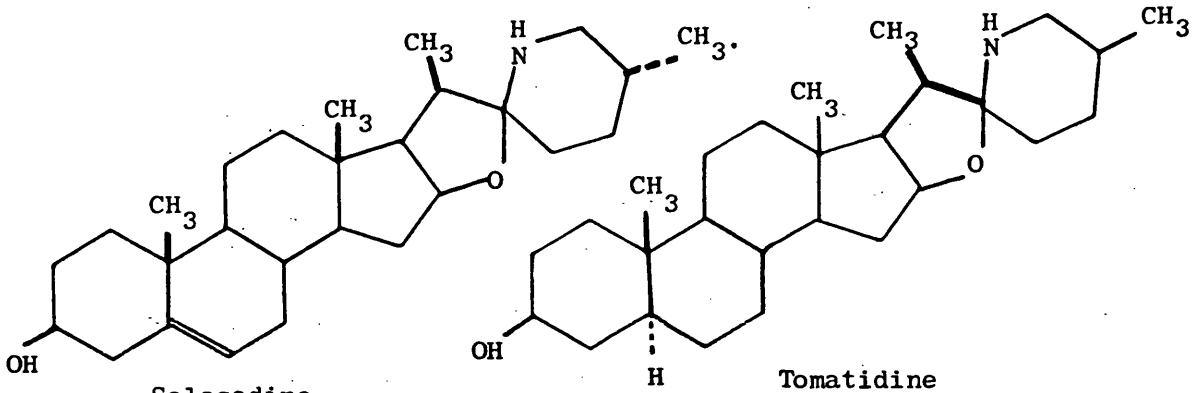
Many species of Holarrhena contain esters or glycosides of alkamines called the Kurchi alkaloids which include holarrhimine(36), conarrhimine(37), and conkurchine(38). The bark of the kurchi shrub has been used as a remedy for amoebic dysentery in India.

Ten years ago,[105,106] the active steroid alkaloidal components from the Columbian arrow poison frog - Phyllobates aurotaenia were separated and some of which were characterised[107] as batrachotoxinin A(39), batrachotoxin(40), and homobatrachotoxin(41). Batrachotoxin[105] is an active cardiotoxin, affecting neuromuscular preparations both pre- and post-synaptically, nerve axons, superior cervical ganglion, and Purkinje fibres in the heart, due to the selective and irreversible increase in membrane permeability to sodium ions.[108]

2.2.1.2

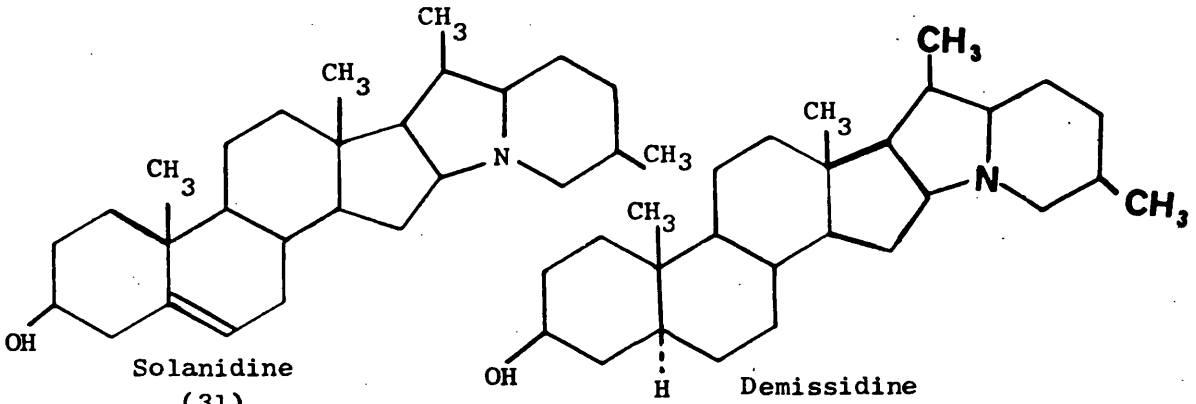
Azasteroids with nuclear nitrogen have been isolated by Schöpf and Braun[102] from the venom produced by the parotid and skin glands of the Salamanders.[103] Samandarine(42) is a central nervous system convulsant. The related ketone samandarone(43) has also been isolated.[100]

Azasteroids such as A25822B(44) with high antifungal activity have been isolated from the crude fermentation broth of the fungus Geotrichum flavo-brunneum.[109]



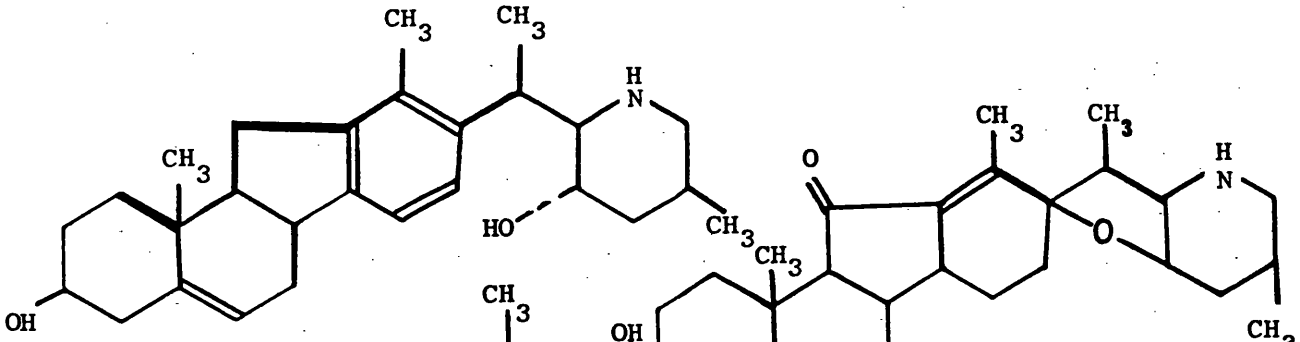
Solasodine
(29)

Tomatidine
(30)



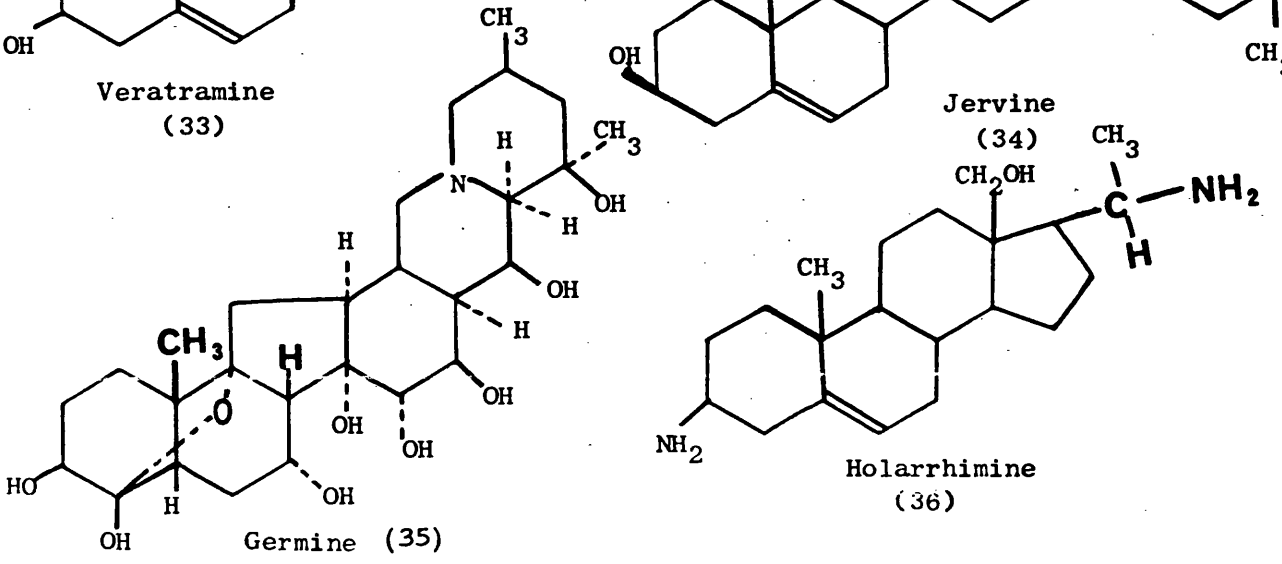
Solanidine
(31)

Demissidine
(32)



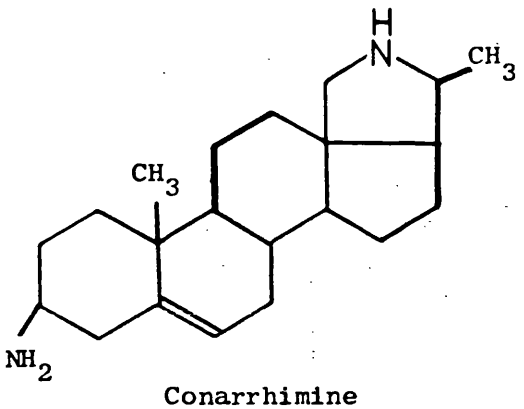
Veratramine
(33)

Jervine
(34)

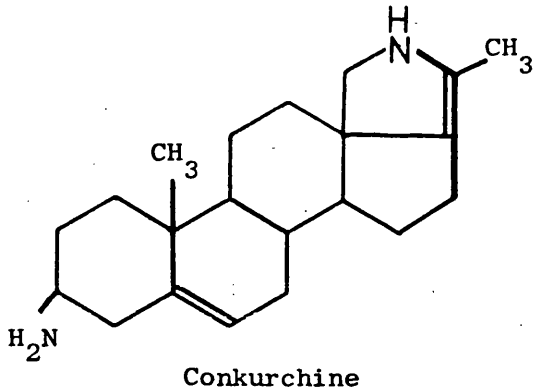


Germine (35)

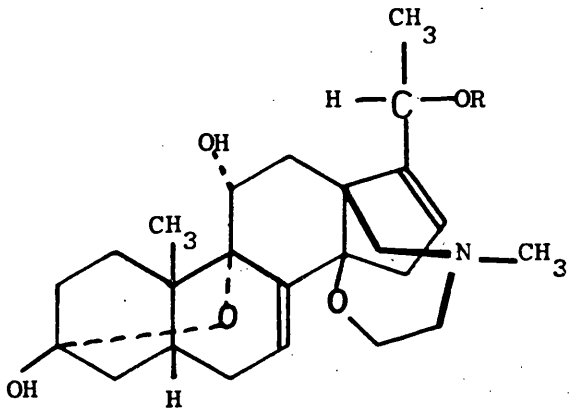
Holarrhimine
(36)



Conarrhimine
(37)

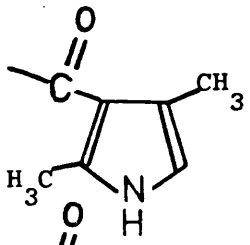


Conkurchine
(38)

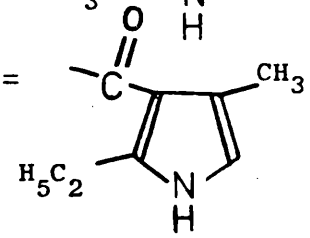


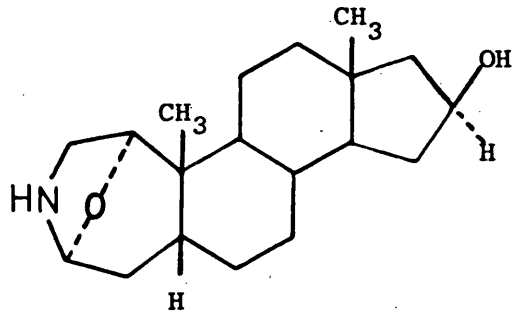
(39) R=H

(40) R =

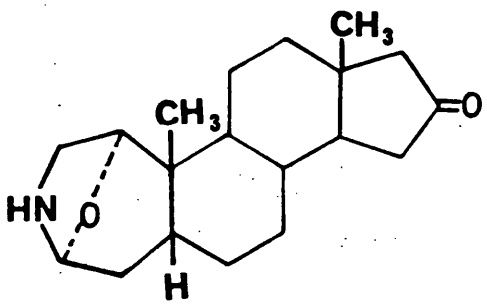


(41) R =

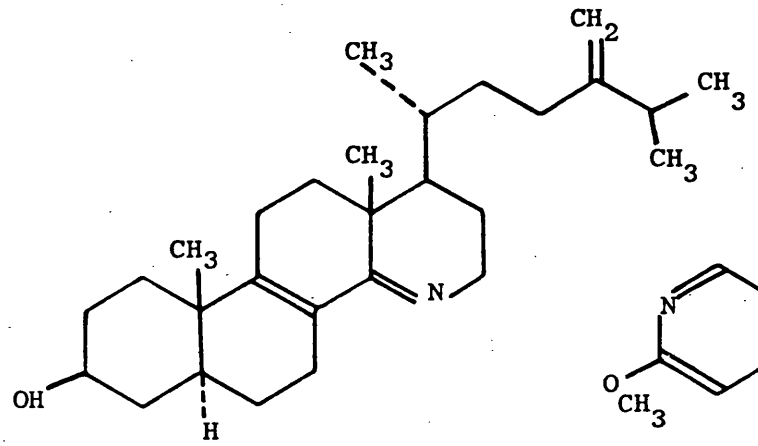




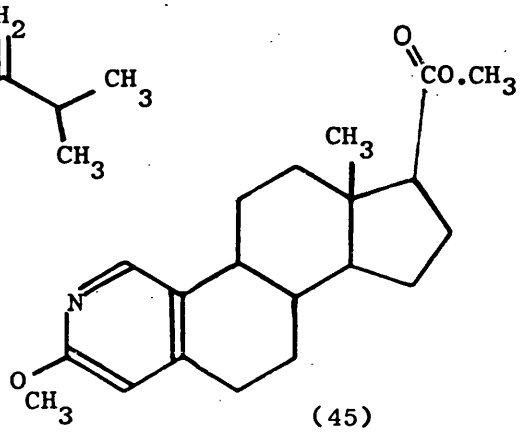
Samandarine
(42)



Samandarone
(43)



(44)



(45)

A25822B

2.3 Syntheses of azasteroids

Many azasteroids of purely synthetic origin have been prepared by total or partial synthesis. Modified steroids have attracted a great deal of attention for three main reasons:-

(i) their preparation is a stimulating challenge to the organic chemist, often involving development of new and generally useful reactions;

(ii) the investigations of reaction mechanism and stereochemistry based upon the steroidal framework, provide significant and interesting chemical problems; and

(iii) biological properties of modified steroids are of great interest.

2.3.1 Aza analogues of the naturally occurring steroids

Many genuine hetero analogues of naturally occurring hormones have been synthesised, including:
2-azaoestradiol 3-methyl ether 17-acetate(45),[110,111] (±)-2-aza-oestradiol 3-methyl ether,[111] (±)-6-azaoestradiol 3-methyl ether(46),[112] (±)-6-azaoestradiol,[112] (±)-6-azaoestrone,[112,119] (±)-6-azaequilenin (47),[112] (±)-8-azaoestradiol(48),[113] (±)-8-azaoestrone,[113,114] 16-azaoestrone methyl ether(49),[115,116] (±)-16-azaoestrone,[115] 17-azaprogesterone(50),[117] and, 4-azaoestradiol 17-acetate.[118]

2.3.1.1

Pappo and Chorvat[111] synthesised a number of 2-aza steroids following the discovery of a favourable anabolic:androgenic ratio in 17α-methyl-2-oxa-5α-androstan-3-one. Several other 2-aza steroids have been synthesised by Kashman and Kaufman.[120]

2.3.1.2

Several synthetic methods for the preparation of 4-heterosteroids have been established by extensive research in the decade 1960-1970. The 4-Aza-androstane derivative (51A) which has been synthesised from 17β-isopentyloxy-4-androsten-3-one, is reported to have high antimicrobial activity.[121] Earlier,[122] antifungal activity of the 4-azasteroid(51B) had been

observed. The synthesis of 3-deoxy-4-azaoestradiol(52) has been achieved[123] by ozonolysis of 19-nortestosterone, DIBAL reduction of the resultant mixture of enol-lactones to a keto-aldehyde followed by hydroxylamine cyclisation.

2.3.1.3

Bridgehead 5-aza steroids (55) and (56) have been synthesised[124] from the corresponding oximes (53) and (54).

2.3.1.4

7-Cyano-6-azacholestane(57) has been obtained[125] from cholest-5-ene, and 6-aza-3-t-butoxycholestane(59) was prepared by reduction of the amide(58).

2.3.1.5

Engel[126,127] has successfully prepared the 11-azapregnanes(61) and (62). Compound (61) possessing the unnatural 9β-H configuration was obtained *via* the azido acetate(60).[126] 11-Azaoestrogens (64) and (65) were obtained by Badanova and Pivnitskic[128] from the seco-acid(63).

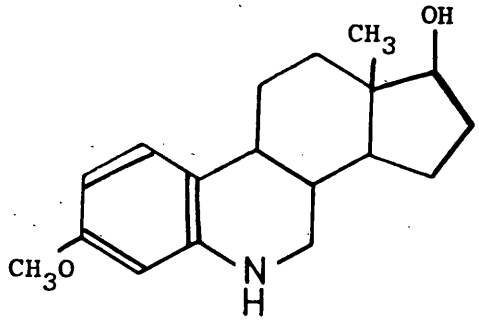
2.3.1.6

Counsell *et al.*[129] reported the synthesis of the 17α-epimer of 20,25-diazacholesterol(66), in continuation of earlier work on the hypocholesteromic activity of various side-chain aza- and diaza-cholestanes. 25-Azalanostane(67) was also prepared by Counsell *et al.*[130] Neither the diaza-compound (66) nor the aza-compound (67) possess significant biological activity.

2.3.2 Partial syntheses of nuclear azasteroids

Insertion of nitrogen atom(s) into the steroid nucleus

Many steroidal analogues containing a nitrogen atom in one of the rings A, B, C, or D have been prepared owing to their importance as synthetic intermediates and because of their enhanced biological activity. Earlier attempts to synthesise azasteroids were primarily for charact-



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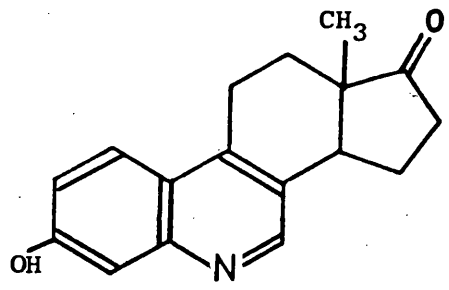

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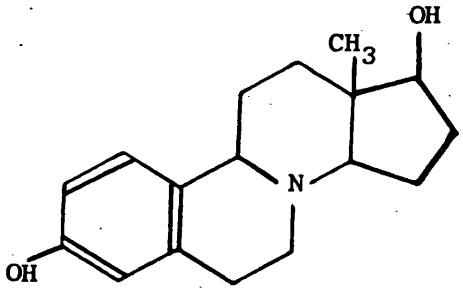

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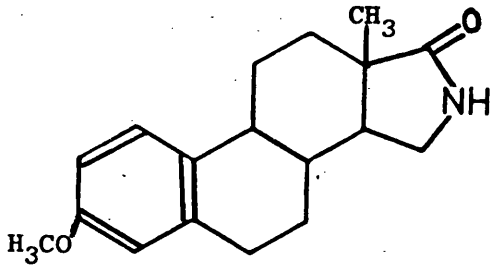

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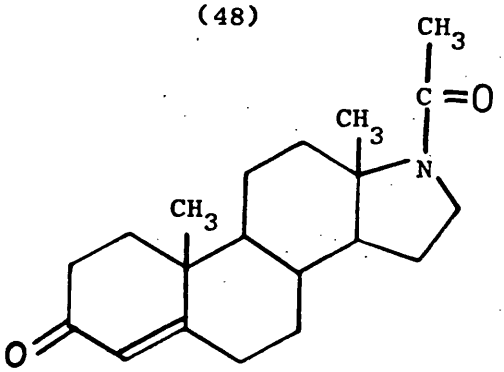

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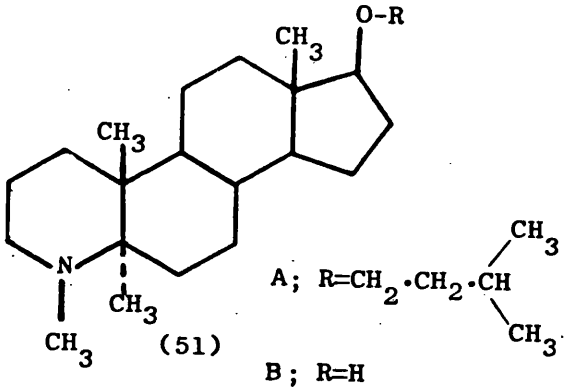
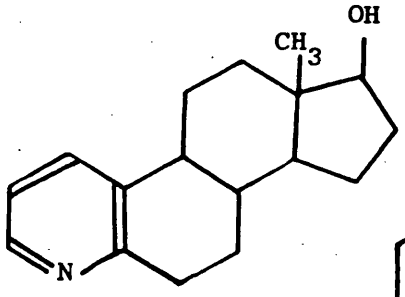


A; R=$CH_2 \cdot CH_2 \cdot CH(CH_3)_2$

B; R=H

(51)



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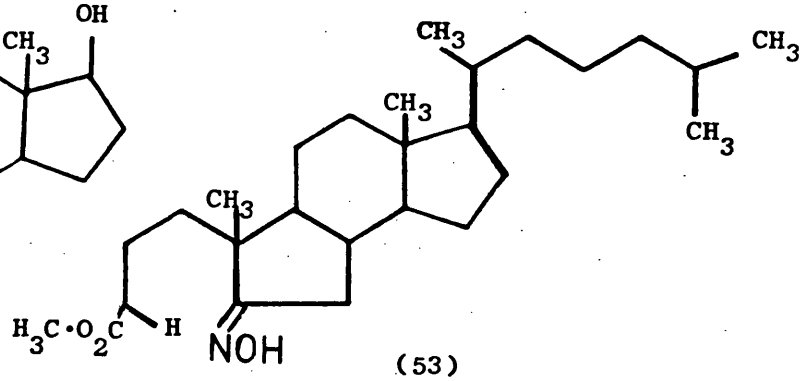

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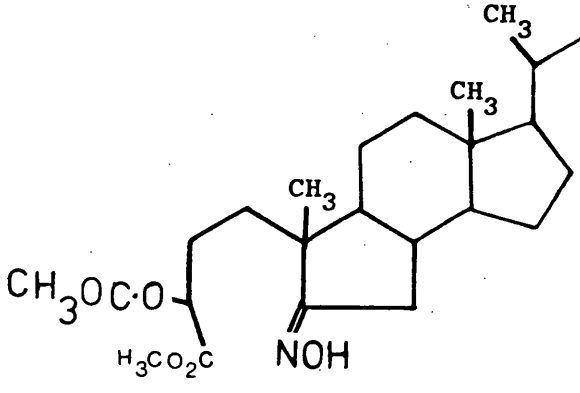

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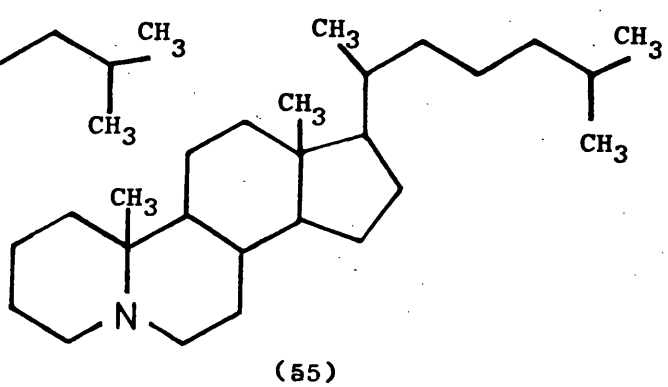

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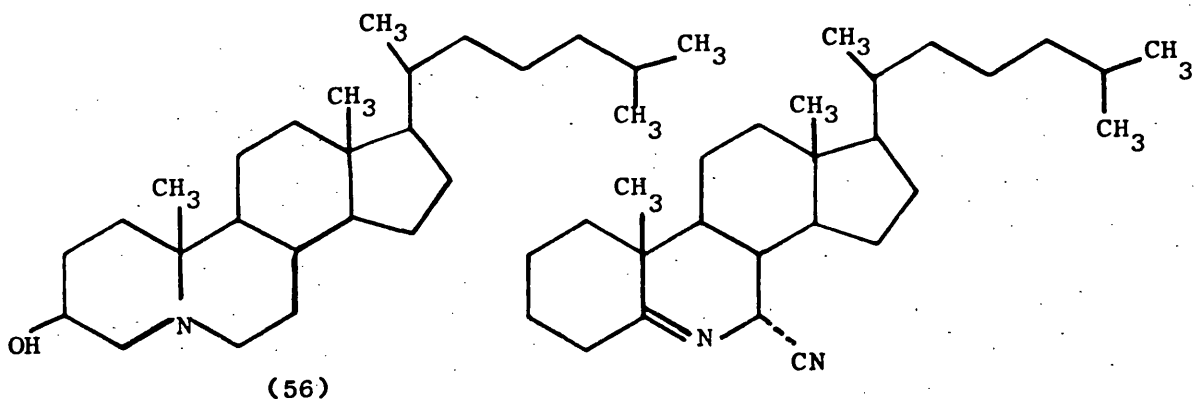
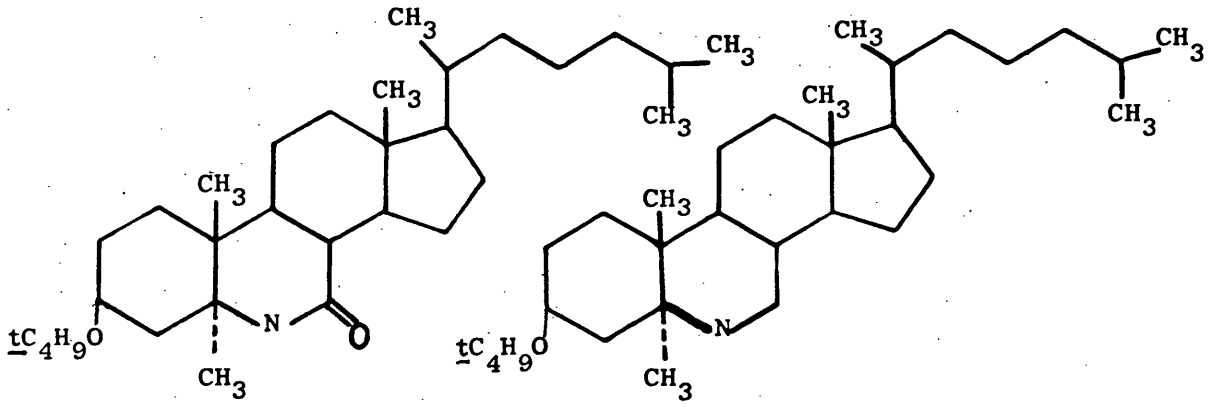


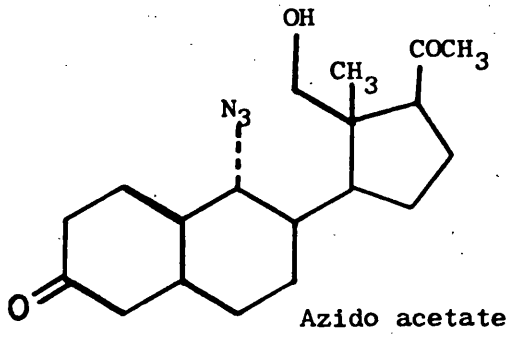
(56)

(57)



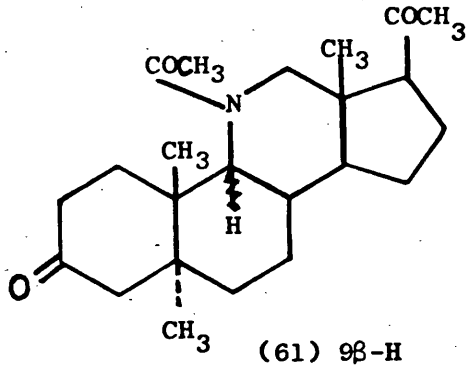
(58)

(59)



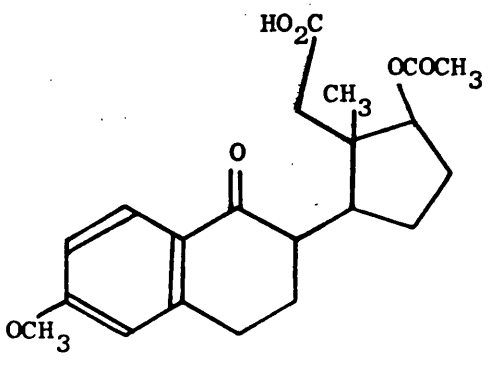
Azido acetate

(60)



(61) 9β-H

(62) 9α-H



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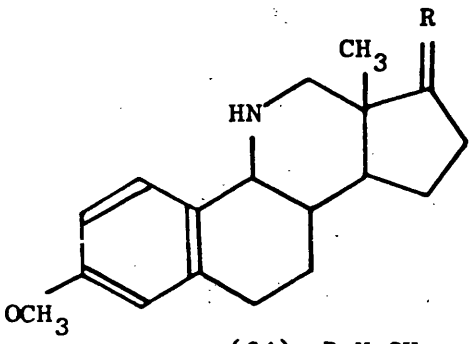
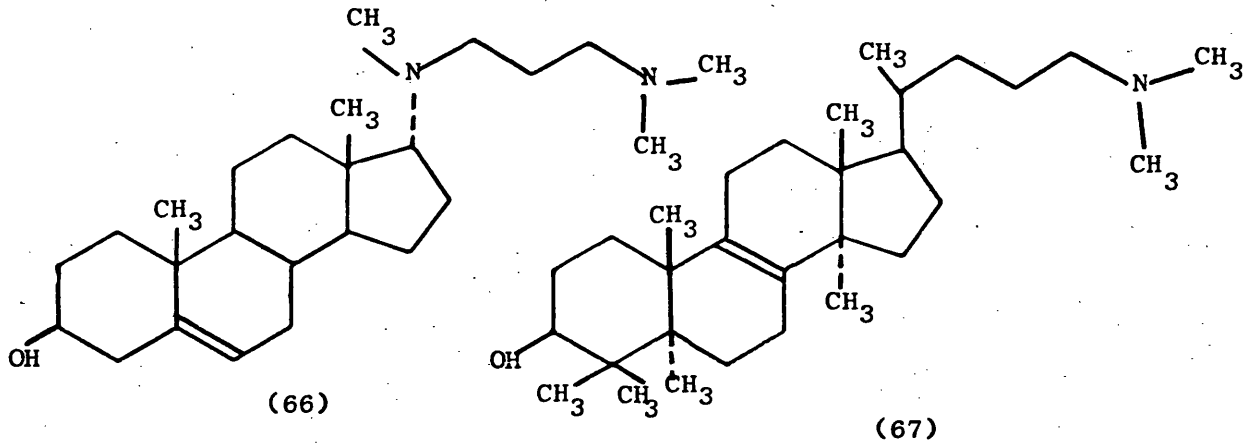


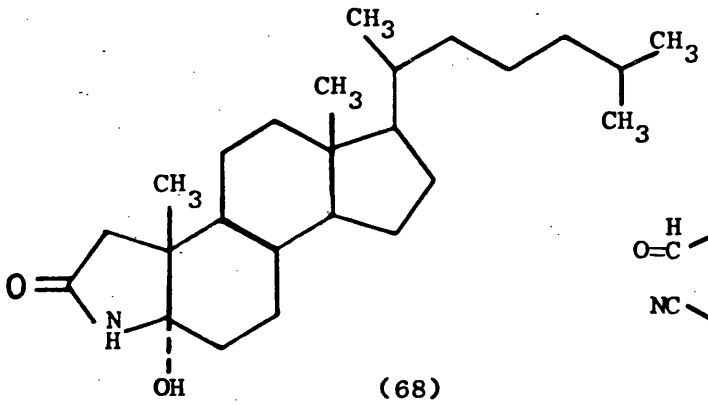
(64) R=H,OH

(65) R=O



(66)

(67)



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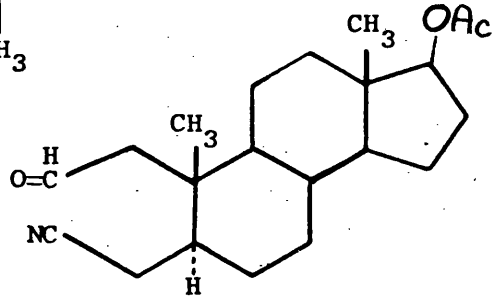

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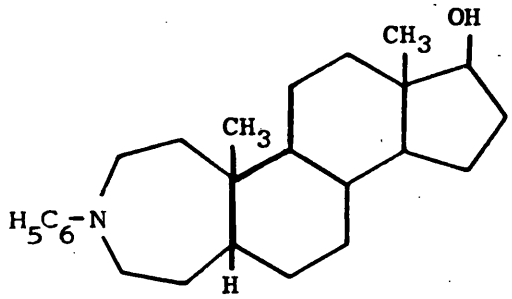

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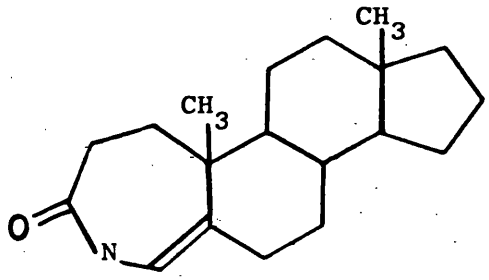

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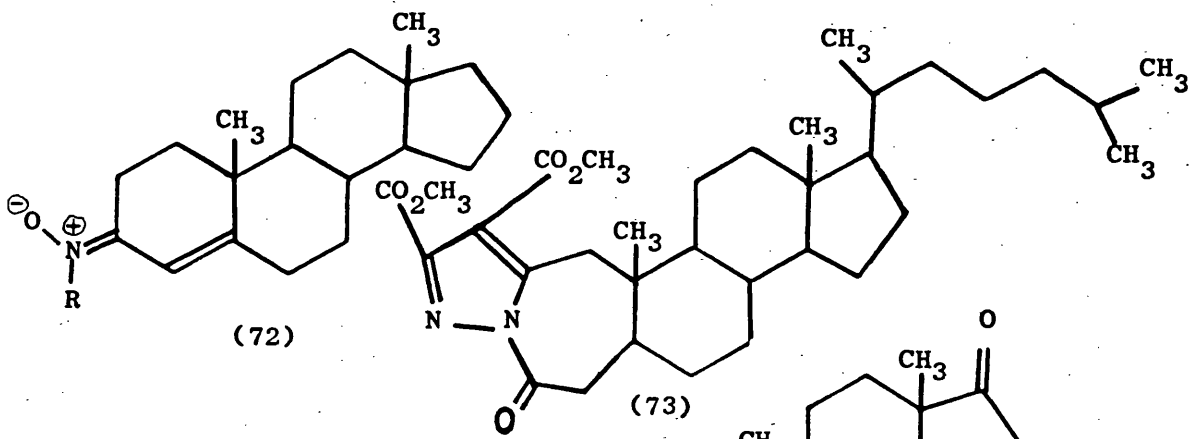
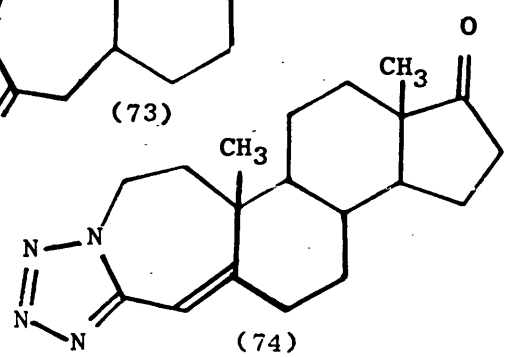


(72)

(73)



(74)

erisation purposes. Systematic work in this field began in the early 1940's and the largest portion of azasteroids have been synthesised in the last twenty years. Several nitrogen analogues of biologically active naturally occurring steroids were found to retain some or all their activity.

2.3.2.1 Ring A modified azasteroids

Cooper and Moore[131] synthesised 2-oxo-3-aza-A-nor-cholestane(68).

Whilst working on the synthesis of salamander alkaloids, Rao and Weiler[132] achieved regioselective Beckmann fragmentation between C-2 and C-3, by making use of the 2-OAc group of 2β,17β-diacetoxy-5β-androstan-3-one to obtain the cyanoaldehyde(69), which was converted into N-benzoyl-3-aza-A-homo-5β-androstane(70) by reduction with diborane followed by cyclisation with one equivalent of benzoic anhydride in pyridine.

Barton *et al.*[133] prepared 4-aza-A-homo steroids(71) *via* modified Beckmann reaction involving p-toluenesulphonyl chloride/pyridine induced rearrangement of nitrone(72). Neumann and Buchecker[134] obtained the steroidal pyrazole(73) by treating 2-diazocholestan-3-one with dimethyl acetylenedicarboxylate.

In view of the biological activity displayed by several tetrazoles, the tetrazolo steroid(74) was synthesised from (25R)-spirost-4-en-3-one by Singh *et al.*[135] *via* BF_3-HN_3 treatment, followed by degradation of the spiro structure.

Starting from A-nortestosterone, Levine[136] accomplished the incorporation of a β-lactam ring into a steroid molecule. The removal of a carbon atom from ring A by oxidation ($NaIO_3$, $KMnO_4$), followed by introduction of a nitrogen atom by C-5 oximation and subsequent Beckmann rearrangement to produce a B-homo ring, and finally removal of the amide oxygen and dicyclohexylcarbodiimide (DCC) ring closure of the amino acid(75) furnished the β-lactam androstane(76a). The pregnane analogue (76b) was similarly prepared.[137]

2.3.2.2 Ring B modified azasteroids

Aza-B-homo steroids have been extensively studied and are usually prepared *via* Beckmann and Schmidt reactions of 6- and 7-oximes. Suginome and Takahashi[138] synthesised 6-aza-B-homo-5α-cholestan-7-one and 7-aza-B-homo-5α-cholestan-6-one and the corresponding 5β-derivatives *via* photo-Beckmann rearrangement of 5α- and 5β-cholestan-6-one oximes. As the migration of the carbon centre proceeds, configuration is retained *via* the oxaziridine intermediate. The photolysis[139] of 3α,5-cyclo-5α-cholestan-6-one oxime gave, amongst other products, (77) and (78), in low yields owing to unfavourable conformational factors. Khuong-Huh and Pancrazi[140] studied the decomposition of 6β-azido-3α,-5α-cyclopregnane in order to investigate the eventual insertion of a nitrene intermediate - generated by photolysis of an azido steroid - into an angular methyl group. Detection of the 7-aza-B-homo steroids(79a) and (79b) among the products, indicated a preferential migration of the less strained C-6 ----- C-7 bond. Both the 6- and 7-aza-B-homopregnanes, (80a) and (80b), were formed in the absence of strain, as observed in the photolysis of 6β-azido-5α-pregnane[141] in cyclohexane.

Mitsuhashi *et al.*[142] obtained the lactams (81) and (82) from cholesta-3,5-dien-7-one *via* hydrolysis of the aziridine ring in (83) and subsequent Schmidt reaction.

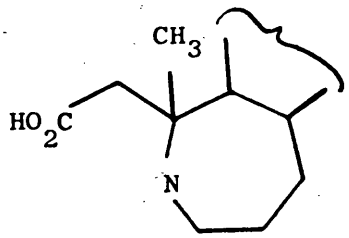
The unusual dimeric triazolosteroids(84) have been prepared by reacting 7α-azido-Δ^5-steroids with a mixture of lead tetraacetate and trimethylsilyl azide ($(CH_3)_3 \cdot SiN_3$) and subsequent catalytic (Pd/C) hydrogenation.[143]

2.3.2.3 Ring D modified azasteroids

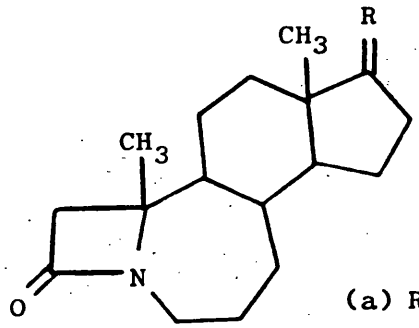
The 17a-aza-D-homo steroids (85a) and (85b)[144,145] can be obtained in low yields by photo-Beckmann rearrangement of androsterone oxime.

Singh *et al.*[146] report the thermal cyclisation of azidonitriles, shown in (86), in the synthesis of bis-tetrazolo steroid(87). The product was formed on treatment of 4-androstene-3,17-dione with HN_3-BF_3 complex.

18-Nor-17a-aza-D-homoandrostane(88) has been synthesised by Diatta *et al.*[147] by ozonolysis of the unsaturated nitrile obtained *via* the Beckmann fragmentation of the 17-ketoxime.

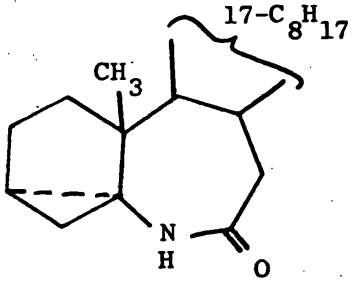


(75)



(a) R=O

(76) (b) R=$COCH_3$; H



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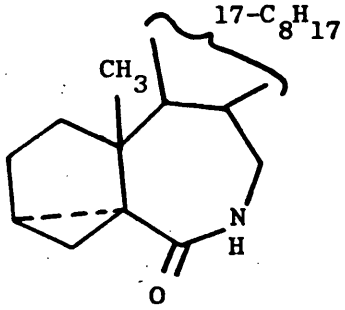

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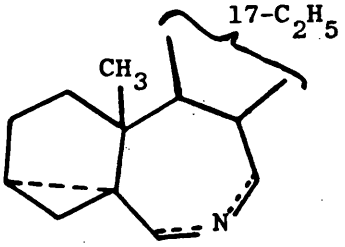
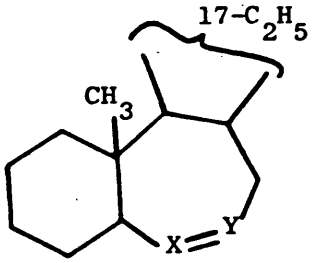


(79)

(a) 5,6-dehydro-

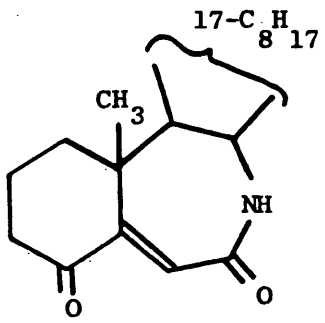
(b) 6,7-dehydro-



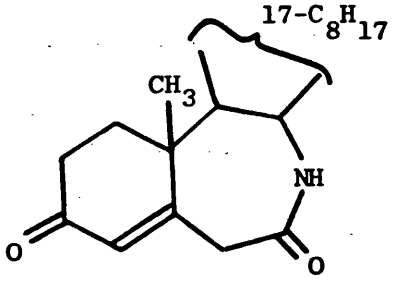
(80)

(a) X=N; Y=CH

(b) X=CH; Y=N



(81)



(82)

2.3.2.4 Bis-azasteroids

The synthesis of bisonium steroids was suggested owing to the neuromuscular-blocking potency in several steroidal quaternary ammonium analogues. Singh et al.[148] report the synthesis of compound (89) from 17a-aza-D-homoandrost-4-ene-3,17-dione via potassium permanganate-sodium iodate ($KMnO_4$-$NaIO_3$) oxidation, formation of the N-benzyl-lactam, debenzylation and sodium-pentanol reduction. Reaction of the bis-amine with formaldehyde/formic acid followed by methyl iodide quaternisation yielded the product (89), which showed biological activity comparable to tubocurarine.

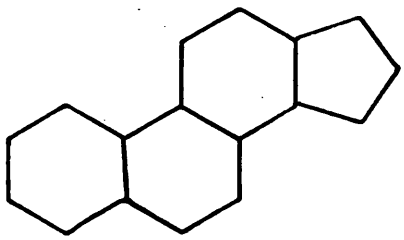
2.3.2.5

The first examples of azasteroids in which a carbon atom common to two rings of the steroid nucleus is replaced by a nitrogen atom, were prepared by Meltzer et al.,[149], and Meyers et al.[150]

A new type of azasteroid, 17-azaprogesterone in which the C. atom bearing the steroid side-chain has been replaced by a nitrogen atom, has been synthesised by Rakhit and Gut.[151]

2.3.3 Total syntheses of nuclear and side-chain azasteroids

A steroid molecule can be constructed by starting with a one- or two-ring moiety and attaching chains to it which are capable of undergoing cyclization. In this manner, the molecule is built up until the four rings are attached to each other in the required chrysene-type orientation.



Several different routes may be employed, including:-

(i) Cyclization of a polyolefin ⟶ ABCD

(ii) AB ⟶ ABC ⟶ ABCD

(iii) AB + D ⟶ ABD ⟶ ABCD e.g. Torgov synthesis

(iv) AB + D ⟶ ABCD e.g. Diels-Alder reaction

(v) A + C ⟶ AC ⟶ ABC ⟶ ABCD

(vi) A + CD ⟶ ACD ⟶ ABCD

(vii) A + D ⟶ AD ⟶ ABCD

(viii) BC ⟶ ABC ⟶ ABCD

(ix) BC ⟶ BCD ⟶ ABCD

(x) B + D ⟶ BD ⟶ ABCD

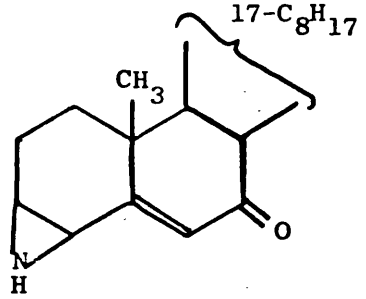
(xi) CD ⟶ BCD ⟶ ABCD

Some of the above mentioned routes are discussed in the following section, but for further details the reader is referred to the text by Blickenstaff, Ghosh and Wolf.[270]

2.3.3.1

Several new methods for the total synthesis of azasteroids have been developed by Huisman et al.[154] Approaches involving enamine reactions have been described by Huisman and Pandit for the synthesis of 13,14-diaza-[155,156] and 11,13-diaza-[157] steroidal systems. (See Scheme 3) The starting material for the 13,14-diaza-D-homosteroid(95) was 6-methoxy-2-tetralone(90). Alkylation of its pyrrolidine enamine resulted in the formation of the α-keto ester(91), which on treatment with perhydropyridazine in boiling xylene yielded the 13,14-diazasteroid (92). Similarly, condensation of (91) with hydrazine hydrate afforded the intermediate (93) which on $LiAlH_4$ reduction gave the tricyclic hydrazine(94).

Pandit et al.,[157] in an alternative approach, synthesised 11,13-diazasteroids utilising the morpholine enamine of 6-methoxy-1-tetralone (96). Acylation of the enamine with the acid chloride of monomethyl succinate, followed by acid hydrolysis, yielded the diketo acid(97). Esterification of the acid (97), and subsequent heating with guanidine carbonate in 2-ethoxyethanol afforded the tricyclic system (98). Catalytic reduction of the latter in an acidic medium yielded the 11,13-diazasteroid(99). Treatment of the diketo acid(97) with hydrazine hydrate led to the formation of the hydrazine salt of (100) which was isolable in the zwitterion form by careful adjustment of its aqueous solution to pH 3.5. Esterification of the acid (100), followed by refluxing with sodium hydride in dioxan afforded the C-nor steroidal structure(101).



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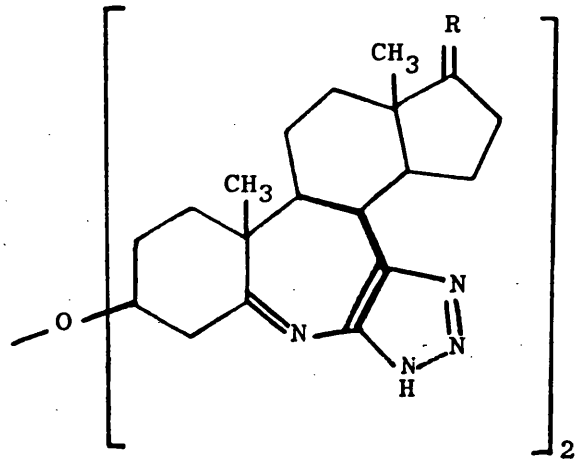

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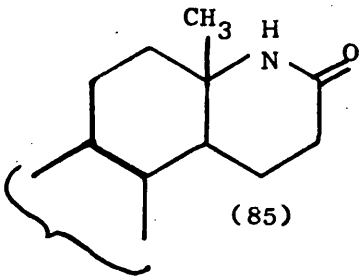
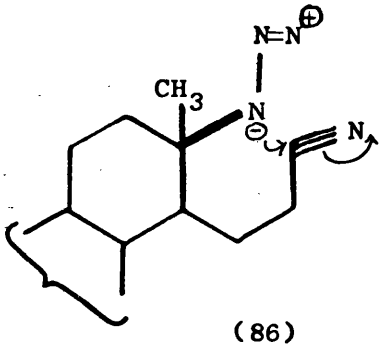


(85)

(a) 13β-Me

(b) 13α-Me



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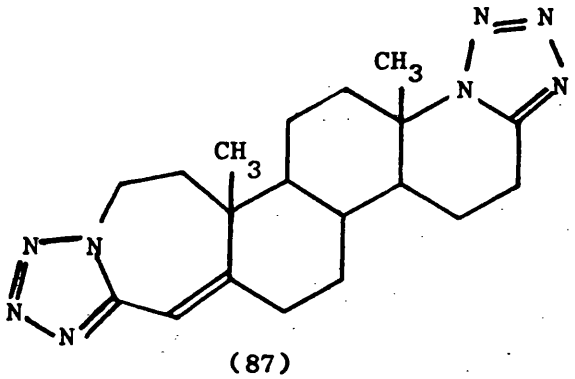

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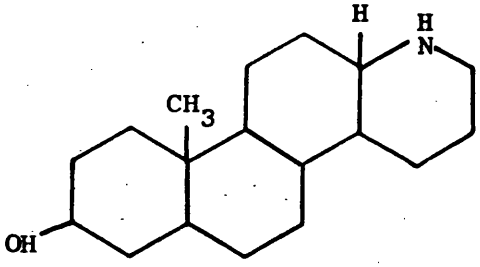

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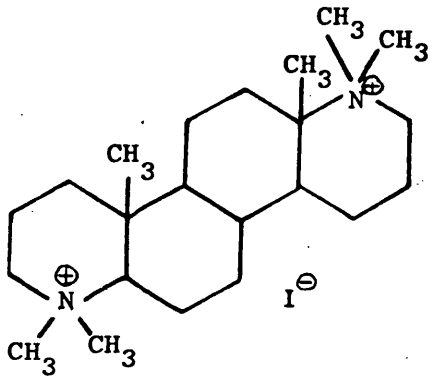
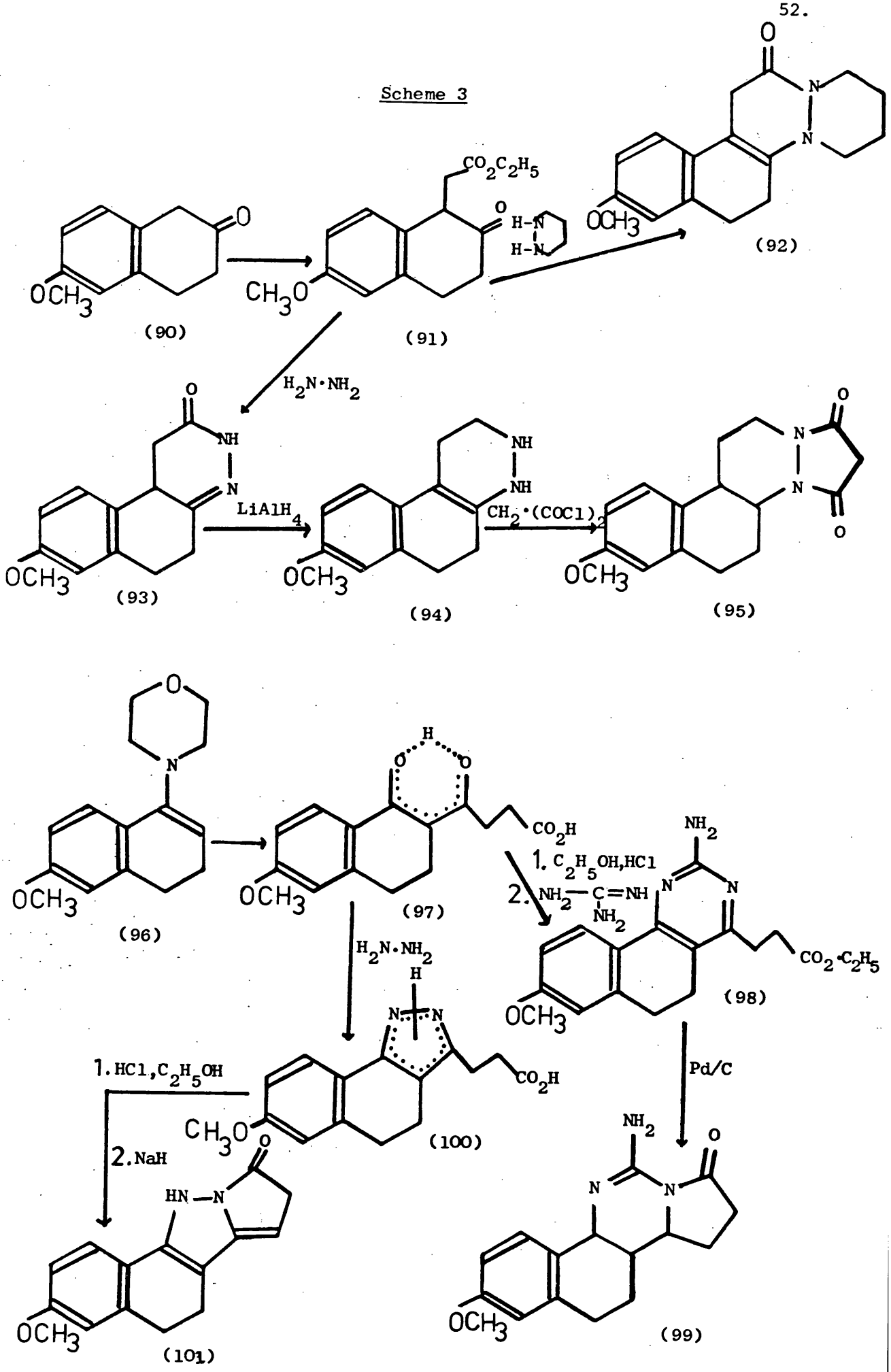


(89)

Scheme 3


(90)
(91)
(92)
(93)
(94)
(95)
(96)
(97)
(98)
(99)
(100)
(101)
$H_2N \cdot NH_2$
$LiAlH_4$
$CH_2 \cdot (COCl)_2$
1. C_2H_5OH,HCl
2. $NH_2-C(=NH)-NH_2$
1. HCl, C_2H_5OH
2. NaH
Pd/C

2.3.3.2 Wilkins[158] employed a versatile approach based on the 'Diels-Alder' type cycloaddition between an imine and a diene, for the synthesis of several azasteroids[159,160a,160b] (see Scheme 4). Condensation of the ethyl biscarbamate(103) (R = R' = R'' = Et) with the diene (102) in the present of BF_3-etherate, yielded the tricyclic ester(104) (R = R' = Et). Owing to the difficulties encountered during the hydrolysis of the carbamate group, further experiments were carried out with the corresponding benzyl biscarbamate(103) (R = R'' = Bz.; R' = Me) and the adduct (104) (R = Bz.; R' = Me) was isolated as crystals by chromatography. The adduct (104), on treatment with acetic acid, can be isomerised to its 8,9-dehydro-isomer(105) (R = Bz.; R' = Me). Decarbobenzoxylation of (104) (R = Bz.; R' = Me) and (105) (R = Bz.; R' = Me), gives on cyclization of the intermediate γ-amino ester, the 8,9-dehydro-13-azaoestrone (106). The ester (104) (R = Bz.; R' = Me) can also be converted into the 13-azaoestrone(107), by hydrogenolysis of the benzyl ester and catalytic hydrogenation of the 9,11-double bond, followed by cyclization.

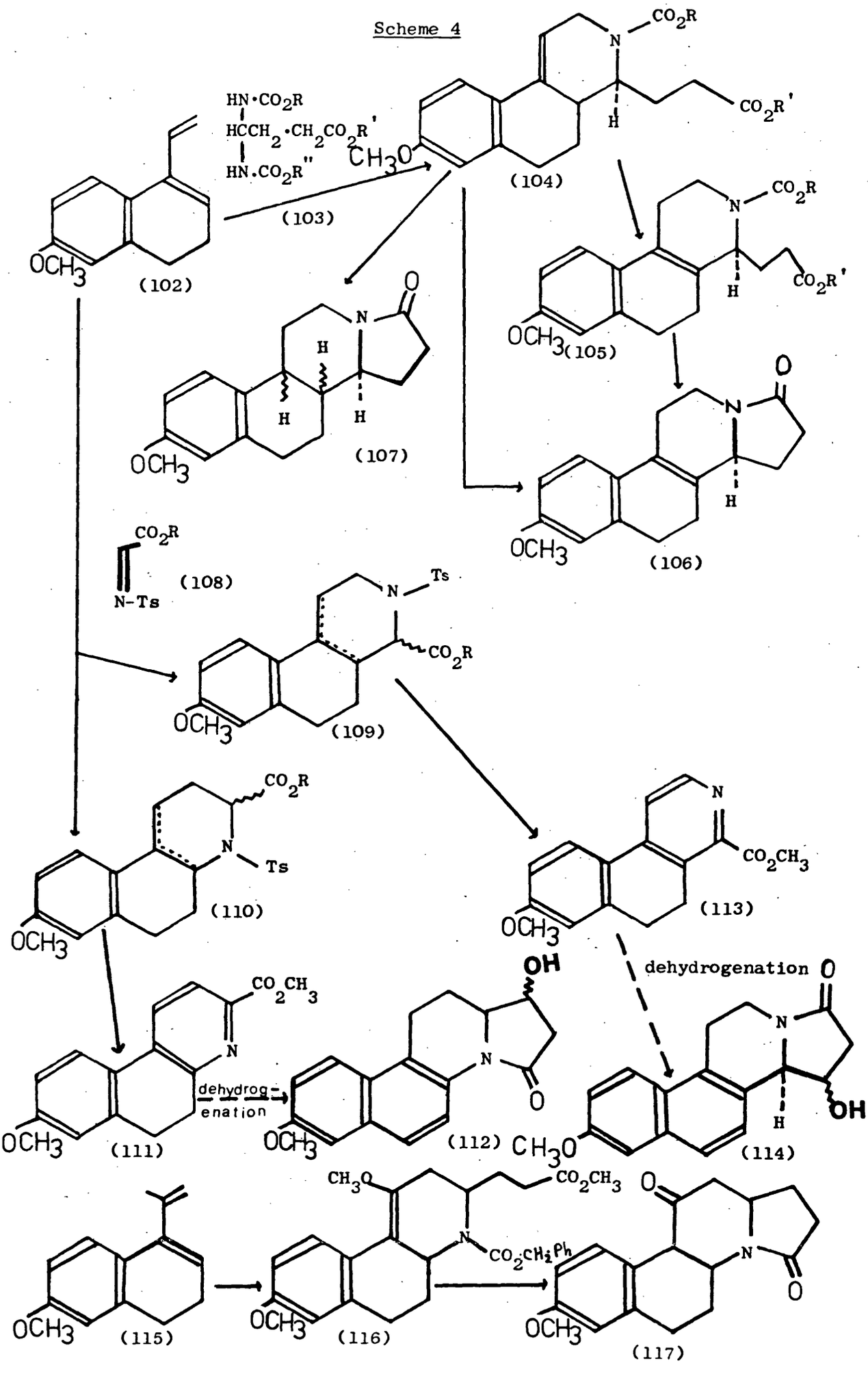
Treatment of the diene(102)[159] with the imino ester(108) leads to a mixture of tricyclic isomeric adducts (109) and (110). Alkaline hydrolysis of the mixture containing (109) and (110) yields the dihydrobenzoquinoline acids, which on separation followed by esterification give the methyl esters (111) and (113). The 14-aza- (112) and 13-azaequilenin (114) systems can be readily obtained from the methyl esters (111) and (113) respectively.

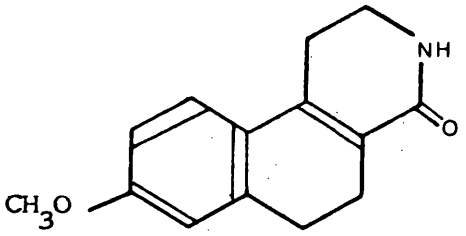
Condensation of diene (115) with the biscarbamate(103) (R = R'' = Bz.; R' = Me) yields predominately the 14-azaisomer(116), from which the 14-azasteroidal system (117) can be obtained by acid-catalysed cleavage of the benzyloxycarbonyl group and cyclization. Further modifications of this method lead to the synthesis of the tricyclic intermediates (118)[161] and (119).[162]

2.3.3.3

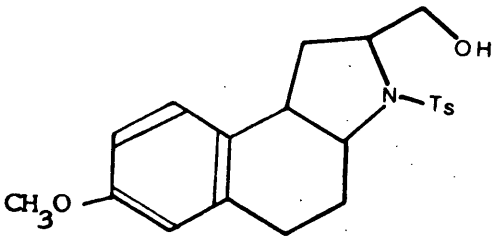
Kessar et al.[163] accomplished the synthesis of the 13-aza compound (123), (see Scheme 5). The amine (120) (R = H) condenses with β-carbomethoxypropionyl chloride to yield the amide (121), which readily undergoes cyclization with phosphorus oxychloride. The basic material (122) obtained thus, on catalytic hydrogenation and thermal cyclisation

Scheme 4


HN·CO2R
HCCH2·CH2CO2R'
HN·CO2R''
CH3O
(103)
(102)
(104)
CO2R
CO2R'
N
H
OCH3
(105)
(106)
(107)
O
(108)
N-Ts
Ts
(109)
(110)
(111)
(112)
(113)
(114)
CO2CH3
dehydrogenation
OH
(115)
(116)
(117)
CO2CH2Ph

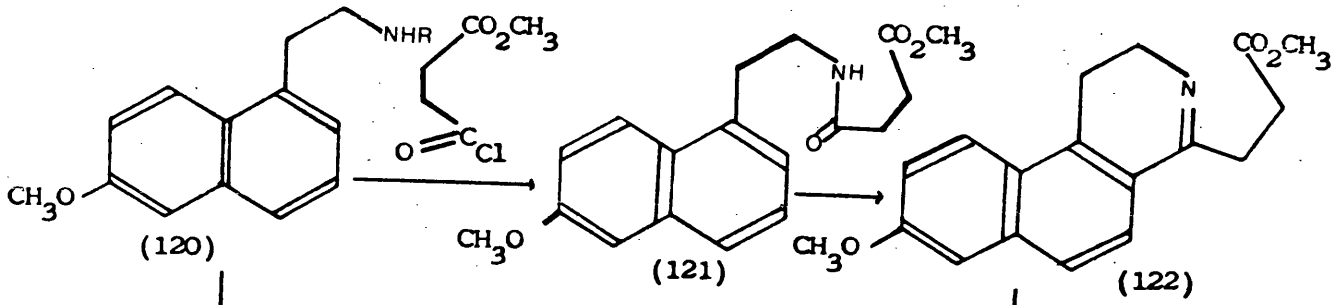


(118)

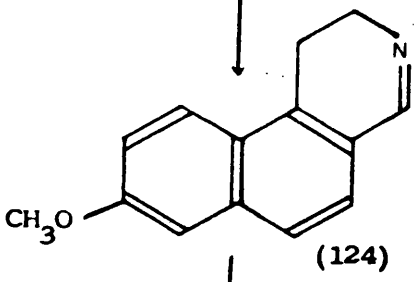


(119)

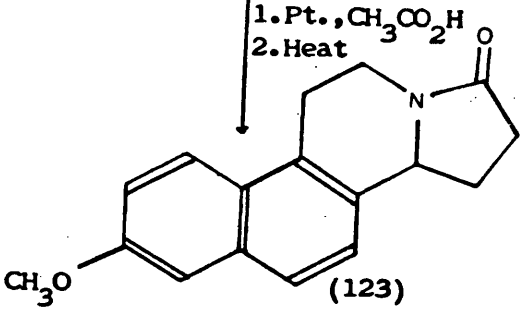
Scheme 5



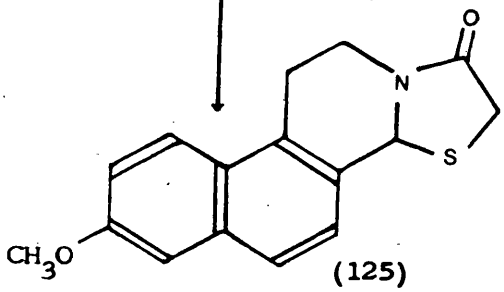
(120) (121) (122)



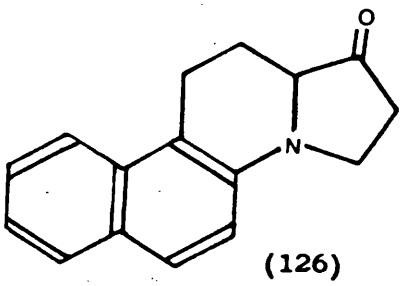
(124)



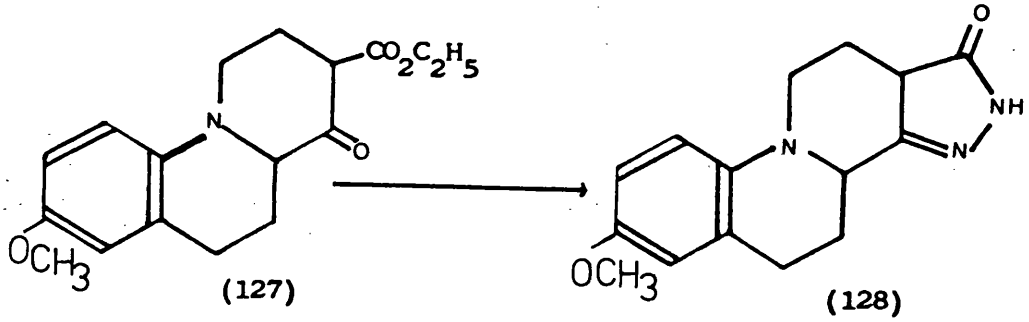
(123)



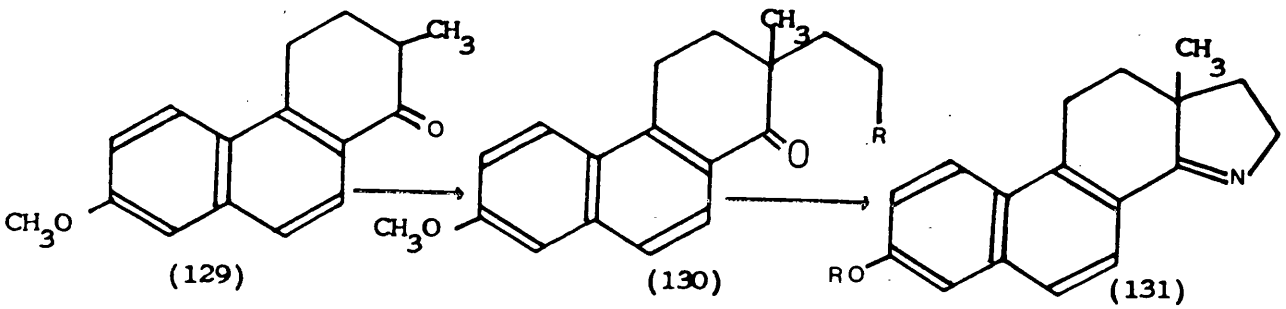
(125)



(126)



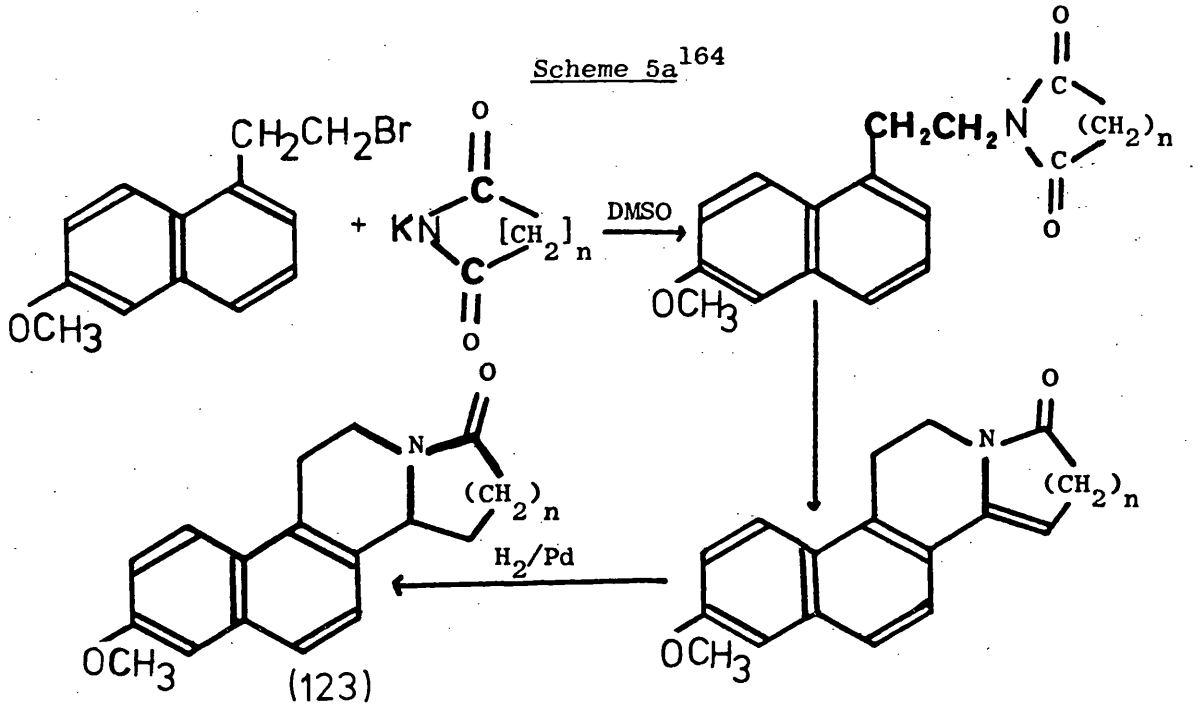
(127) (128)



(129) (130) (131)

leads to 13-aza-18-norequilenin methyl ether (123). The product (123) was also synthesised by Birch and Rao via an alternative route[164] (see Scheme 5a).

Scheme 5a[164]



The amine (120) (R = H) has also been employed[165,166] for the synthesis of 13-aza-15-thia-18-norequilenin methyl ether (125). The amine (120) (R = H) reacts with ethyl formate to give the amide of (120) (R = CHO), which on cyclisation forms the dihydrobenz(f)isoquinoline (124). The thiazolidone (125) is obtained by reacting the isoquinoline (124) with mercaptoacetic acid.

The total syntheses of several 6-azaoestrogens have been described by Speckamp et al.[112]. Jones and Wood,[167-9] and, Schleigh and Popp[170] attempted the synthesis of 9-azasteroids. Both groups report the successful preparation of the tricyclic intermediate (127), but attempts to build up ring D were unsuccessful. When the keto ester (127) is treated with hydrazine, the pyrazolone (128) results.

The synthesis of 14-azasteroids was studied by Poirier et al.[171] and Jones.[172] The former group succeeded in synthesising 3-deoxy-18-nor-14-azaequilenin (126).

Morgan and co-workers,[173] in another series of studies, prepared the known tricyclic ketone (129), which on condensation with acrylonitrile

in t-butyl alcohol in the presence of potassium hydroxide gives the nitrile(130) (R = CN). Hydrolysis of the nitrile(130) (R = CN) furnishes the acid(130) (R = CO_2H), which can undergo a modified Curtius rearrangement to yield the steroidal imine ether(131) (R = Me). When the steroidal imine(131) (R = Me) is heated in the presence of hydrobromic acid, the 15-azaequilenin derivative(131) (R = H) is obtained.

2.3.3.4

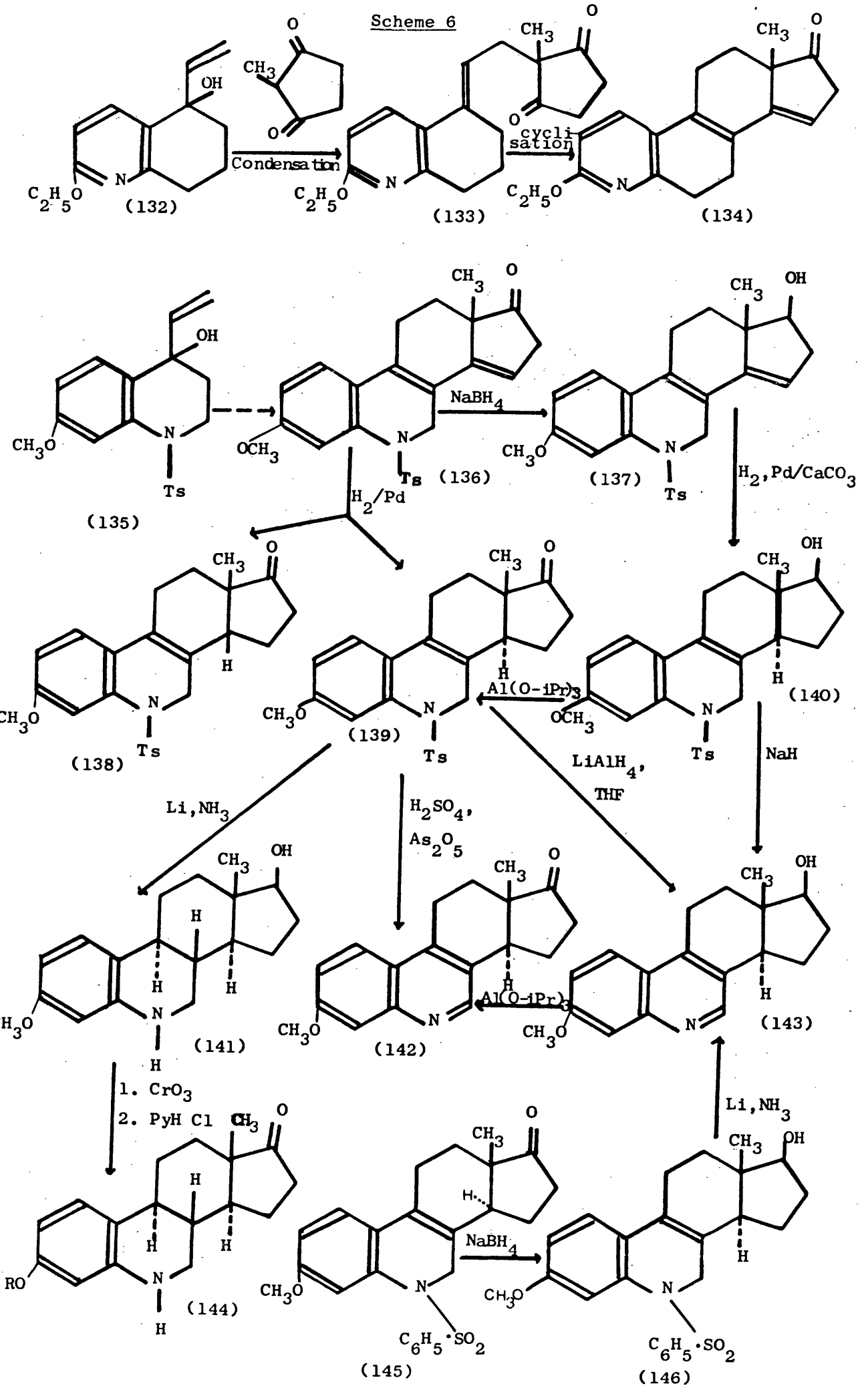
Morgan et al.[174] also report the synthesis of 15,16-diazasteroids. The synthesis of several other diazasteroid derivatives have been reported; for example: 12,14-[175]; 13,16-[176]; 14,16-[176,177]; and 15,16-diazasteroids.[174,178]

Stanovnik et al.[179] have prepared 11-amino-12,13,15,16-tetraaza-1,3,5(10),8,11,14,16-gonaheptaen and other tetraazasteroids and a pentaazasteroid by an ABC $\longrightarrow$ ABCD route.

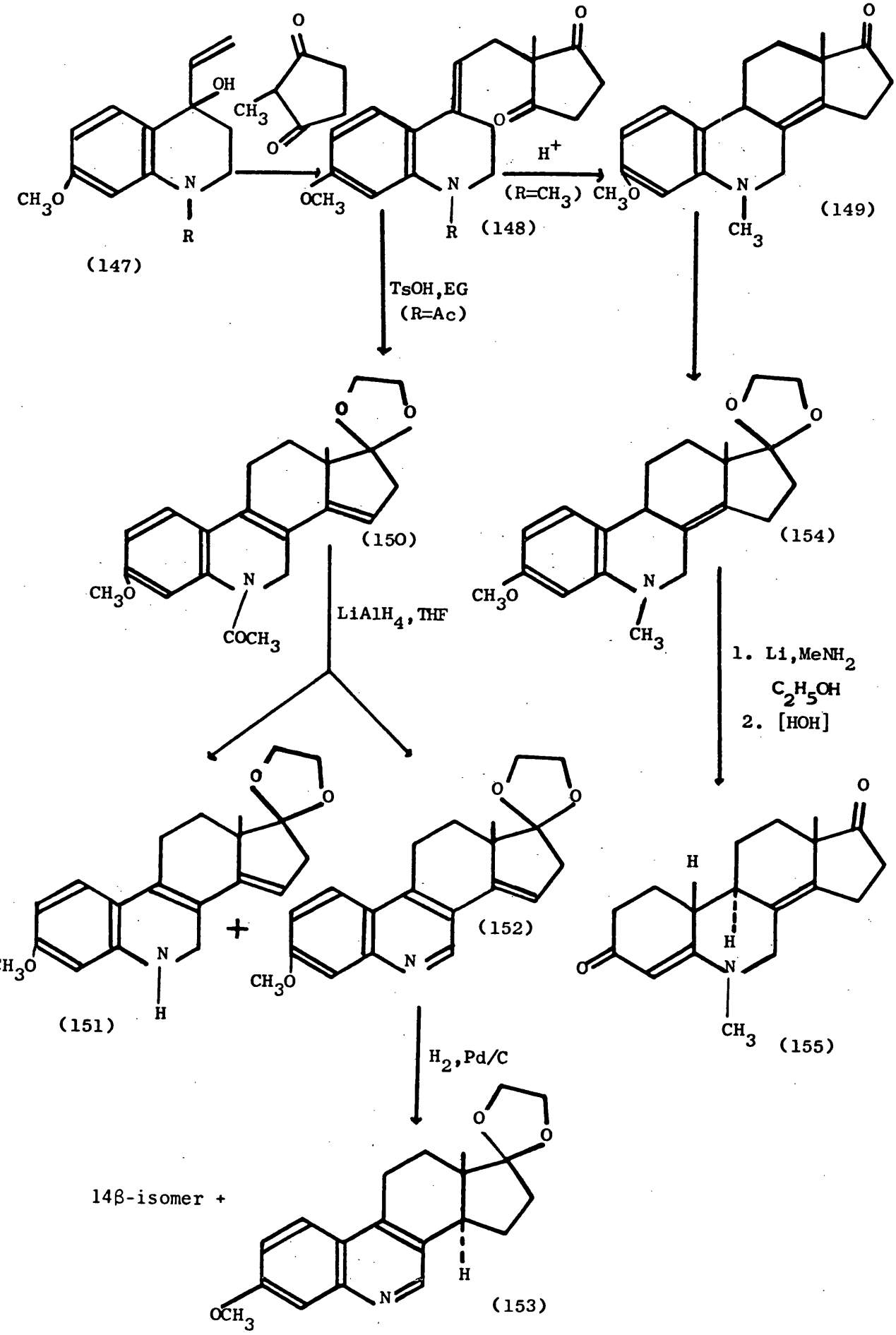
2.3.3.5

The Torgov synthesis (AB + D $\longrightarrow$ ABD $\longrightarrow$ ABCD) has been employed for the preparation of many azasteroids, (see Scheme 6). Condensation of the vinyl alcohol(132) with the cyclopenta-1,3-dione, followed by cyclization affords the azasteroid(134). N-Arylsulphonyl pentaene intermediates with tosyl(136)[179a,180] or benzenesulphonyl[119,182] substituents can be synthesised from the requisite allylic alcohols, e.g.(135). Catalytic hydrogenation of the benzenesulphonyl analogue gives the CD-trans tetraene,[182] but with the tosyl analogue(136) a mixture predominating in the 14 β-isomer(138) results.[112] Hydrogenation of the 17β-hydroxy analogue(137) yields predominantly the α-isomer(140). Oppenauer oxidation of (140) affords (139) which can undergo ring B aromatization to give the methyl ether(142) of 6-azaequilenin. Alternatively, (142) can be obtained via (143) by detosylation of (140) with sodium hydride or by reacting (139) with lithium aluminium hydride ($LiAlH_4$) in tetrahydrofuran(THF). Lithium-ammonia reduction of the 8,9-double bond occurs in 30% yield to give the methyl ether(141) of 6-azaoestradiol. In the benzenesulphonyl series, however, lithium-ammonia reduction of (146) gives the product (143).[182] 6-Azaoestrone (144) (R = H) was synthesised by oxidation of (141) and demethylation

Scheme 6


Condensation
cyclisation
NaBH4
H2/Pd
H2,Pd/CaCO3
Al(O-iPr)3
LiAlH4, THF
NaH
Li,NH3
H2SO4, As2O5
1. CrO3
2. PyH Cl
NaBH4
Li,NH3
(132)
(133)
(134)
(135)
(136)
(137)
(138)
(139)
(140)
(141)
(142)
(143)
(144)
(145)
(146)

Scheme 7[181]


OH
CH3
O
CH3O
N
R
OCH3
H+
(R=CH3)
(147)
(148)
(149)
TsOH,EG
(R=Ac)
(150)
(154)
COCH3
LiAlH4,THF
1. Li,MeNH2
C2H5OH
2. [HOH]
(151)
(152)
(155)
H2,Pd/C
14β-isomer +
(153)

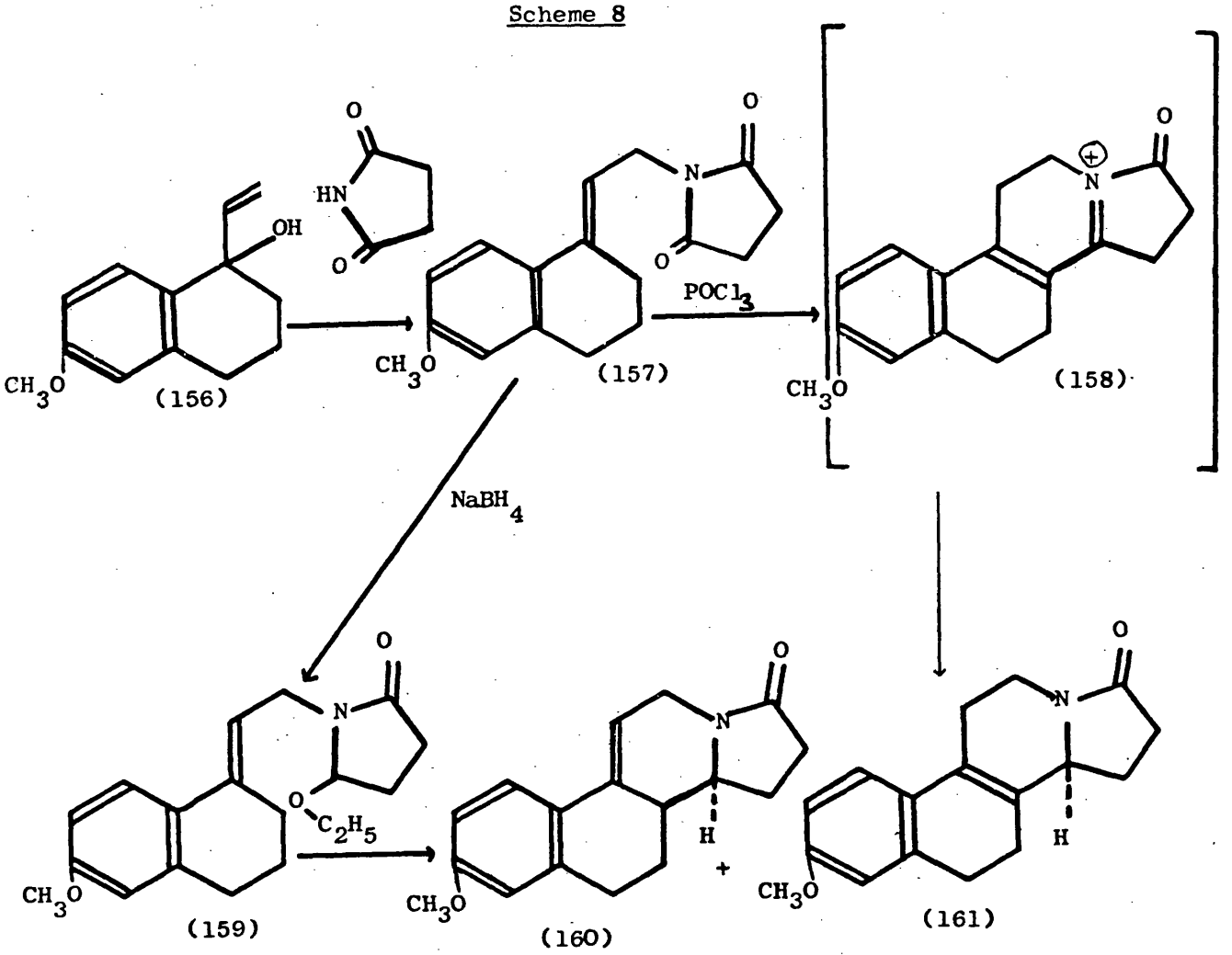
with pyridinium chloride.[183] The 14β-isomers of (141), (142), (143) and (144) have also been prepared.

The N-methyl ABD intermediate (148) (R = CH_3) was prepared from the allylic alcohol(147) and cyclized to give the $\Delta^{8(14)}$-steroid(149).[181] (See Scheme 7.) Reaction of the allylic alcohol(147) (R = H) with 2-methyl-1,3-cyclopentanedione, followed by acetylation afforded the N-acetyl intermediate(148) (R = Ac), which cyclized under conditions of ketalization to give the pentaene(150) in 50% yield. Lithium aluminium hydride reduction of (150) in tetrahydrofuran(THF) resulted in a mixture of the deacetylated products (151) and (152). Hydrogenation of (152) with palladium/charcoal gives a mixture of the 3-methyl ether, 17-ketal(153) of 6-azaquilenin and the corresponding 14β-isomer, chromatographically separable. The 17-ethyleneketal(154) of azasteroid (149) can undergo a Birch reduction in methylamine (the reaction fails in ammonia) to give the dihydro product, which on hydrolysis yields the diketone(155).[184]

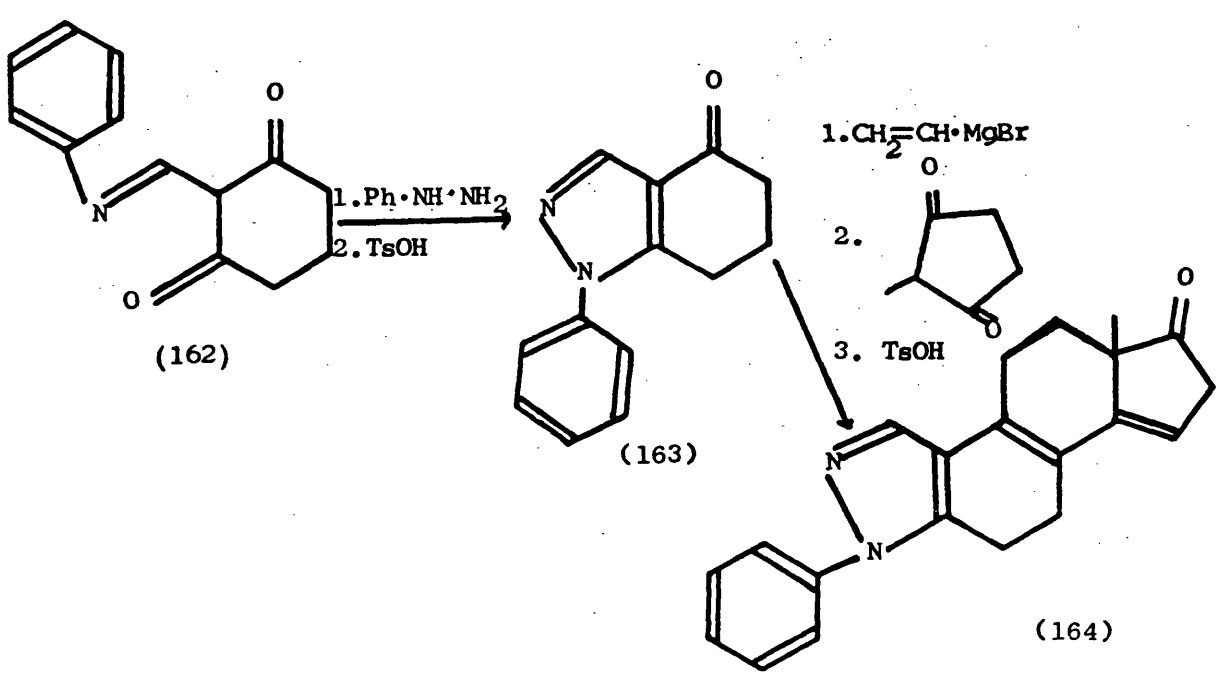
13-Azasteroids can be obtained by replacing the diketone in the Torgov synthesis with succinimide (see Scheme 8). Succinimide reacts slowly with the allylic alcohol(156) in methanol, but more rapidly as a melt containing the potassium salt of succinimide to give the ABD intermediate(157).[185] On treatment with phosphorus oxychloride, the intermediate(157) undergoes cyclization to yield a tetracyclic steroid [probably (158)], which can be hydrogenated over rhodium/charcoal to the methyl ether(161) of 13-aza-8-dehydrooestrone. Alternatively, $NaBH_4$ reduction of (157) in ethanol, containing HCl, results in the ether (159),[186] which on cyclization gives a one-to-one mixture of (160) and (161).

The Torgov synthesis can also be applied to synthesis of steroids with a pyrazole ring A.[187] The allyl alcohol, prepared from the Schiff's base (162), (see Scheme 9), reacts with phenylhydrazine to give the corresponding hydrazone. The latter, on treatment with p-toluenesulphonic acid, undergoes cyclization to yield the pyrazole(163). The allylic alcohol obtained by a Grignard reaction on (163) condenses with 2-methyl-1,3-cyclopentanedione to give the ABD intermediate, which on p-toluenesulphonic acid treatment cyclizes to the diaza-A-nor steroid(164). Sodium borohydride reduction of (164) affords the 17β-hydroxy derivative.

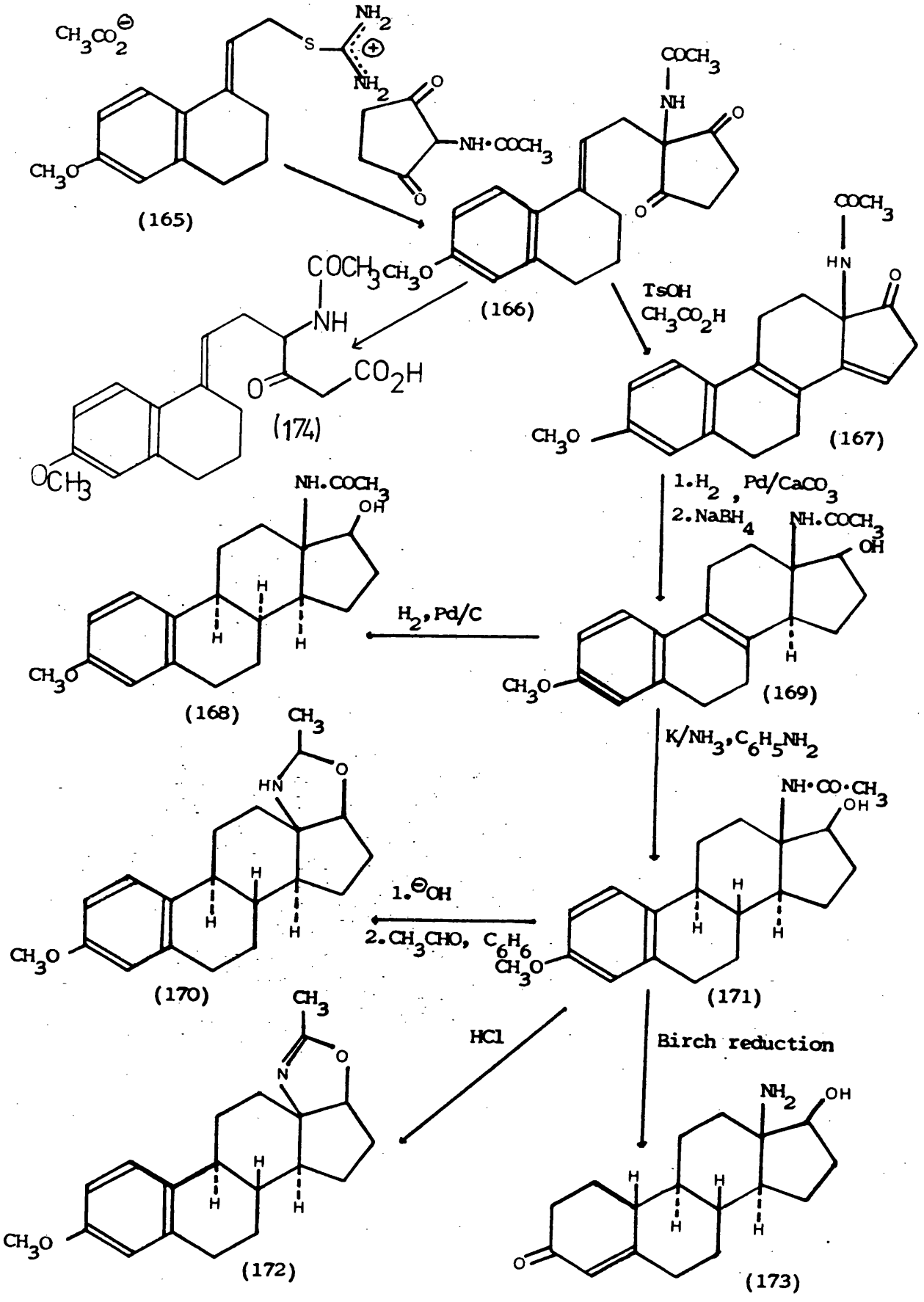
Scheme 8



Scheme 9



Scheme 10


(165)
(166)
(167)
(168)
(169)
(170)
(171)
(172)
(173)
(174)
TsOH
CH_3CO_2H
H_2, Pd/C
1. H_2, Pd/$CaCO_3$
2. $NaBH_4$
K/NH_3, $C_6H_5NH_2$
1. $^{\ominus}OH$
2. CH_3CHO, C_6H_6
HCl
Birch reduction

Some aza-oxa steroids have also been synthesised *via* the Torgov route (see Scheme 10). Condensation of the isothiouronium salt(165) with 2-acetylamino-1,3-cyclopentanedione,[188] followed by cyclization of the ABD intermediate(166) with p-toluenesulphonic acid leads to the steroid (167). Catalytic hydrogenation produces a CD-*trans* geometry as expected, and sodium borohydride reduction of the oxo group gives product (169). Further hydrogenation of (169) results in the 8α-steroid (168). Potassium-liquid ammonia reduction of (169) with aniline as the proton source affords the normal BC-*trans* isomer(171). On treatment with hydrochloric acid, the isomer (171) undergoes ring closure to give the 2-oxazoline(172); the expected N $\longrightarrow$O migration of the acetyl group under such conditions, is not observed. Hydrolysis of the amide(171) followed by condensation of the amino alcohol with acetaldehyde in refluxing benzene, afforded the dihydro derivative(170). 13β-Amino-17β-hydroxy-4-gonen-3-one(173), is obtained by Birch reduction of (171) followed by hydrolysis. Under basic conditions, the ABD intermediate (166) is unstable and undergoes ring D cleavage to form (174).[188]

The thiazole A-ring steroids (see Scheme 11)[189,190] have also been prepared.

2.3.3.6

An 8-azasteroid(185) has been prepared *via* alkylation[191] of 1,5-dimethoxycyclohexa-1,4-diene with the chloride(183) in liquid ammonia, followed by hydrolysis, cyclization with 2N hydrochloric acid, and reduction of the 13-double bond (see Scheme 12). Alkylation of succinimide or glutarimide (potassium salts) with the bromide(189) affords (187) (n = 1 or 2, respectively). Cyclization with polyphosphoric acid, followed by catalytic reduction of the 14-double bond gave rise to the 13-azasteroid(188).[192,193,194]

2.3.3.7

8-Azaoestrone has been prepared *via* the Michael addition of 2-methyl-1,3-cyclopentanedione to the isoquinoline derivative(190) (see Scheme 13). Demethylation of (192) affords 8-azaoestrone.[114,195,196] The methyl ether of 3-hydroxy-6,8-diaza-D-homo-1,3,5(10),6,13-gonapentaen-17a-one has been prepared by a similar route.[197]

Some 14-azasteroids have been prepared by the addition of 2-tetralone(193) to 2-vinylpyridine *via* the formation of the ABD

intermediate(194) (see Scheme 14). Protection of the keto group *via* ethylene ketal formation, catalytic reduction of the pyridine ring, hydrolysis of the ketal, and finally, ring closure gave the prototype(195).[198]

11,14-Diazasteroids have been synthesised *via* the intermediate formed by Michael addition of diethyl (2-naphthylamino)malonate to ethyl acrylate (see Scheme 15).[199]

2.3.3.8

A series of 8-azasteroids have been prepared *via* enamine ABD intermediates. For example, condensation of the isoquinoline derivative(199) with cyclopentanone gives the enamine(200), which can undergo cyclization to yield the 12-keto steroid(201). Methylation followed by catalytic hydrogenation affords the methyl ether(202) of 8-aza-3-hydroxy-1,3,5(10)-oestratrien-12-one.[200,201] The 8-azasteroid (210), (n = 1,2), can be prepared similarly, from the amine ester (209).[202]

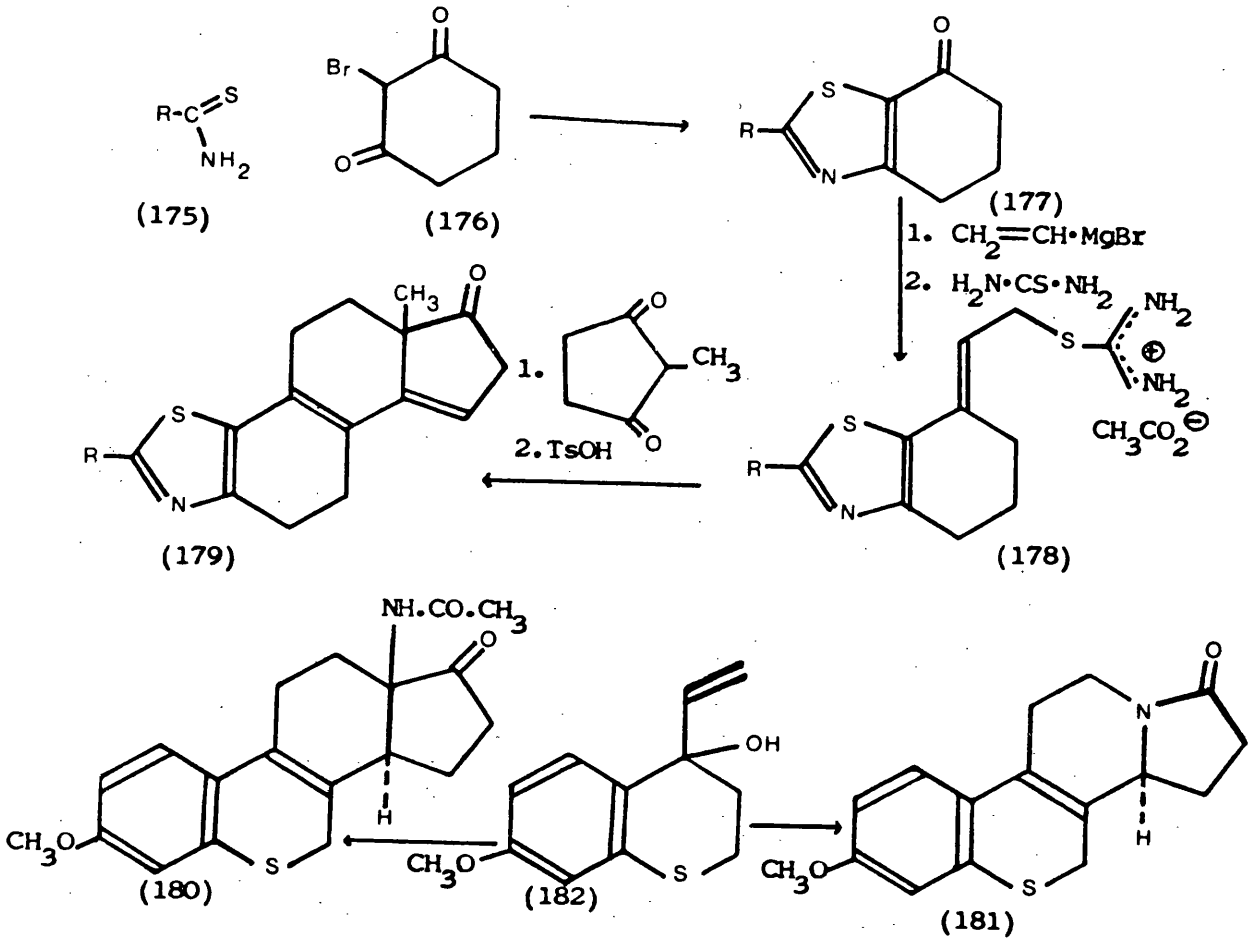
The dihydroisoquinoline(211) (R = H or OCH_3) reacts with β-diketones to give the 8-aza-12-ketosteroids(212) (R = OCH_3, R' = H_2),[203] (R = OCH_3, R' = O)[204] and (213) (R = OCH_3, R' = H_2, Z = NH),[203] (R = OCH_3, R' = O, Z = $C(CH_3)_2$),[203] (R = H, R' = O, Z = $C(CH_3)_2$).[204]

Ethyl bromoacetate alkylation of the enamine(214), followed by acid hydrolysis affords the ester(215), which condenses with perhydropyridazine in boiling xylene to yield the 13,14-diazasteroid(216),[205] (see Scheme 18). The enamine(217) obtained by 1-pyrrolidinocyclopentene addition to methyl 3,4-dihydro-1-naphthoate can undergo hydrolysis (of the ester and enamine groups) to give (218), which can be cyclized to the azasteroids (219) (Z = NH or NCH_2Ph).[206]

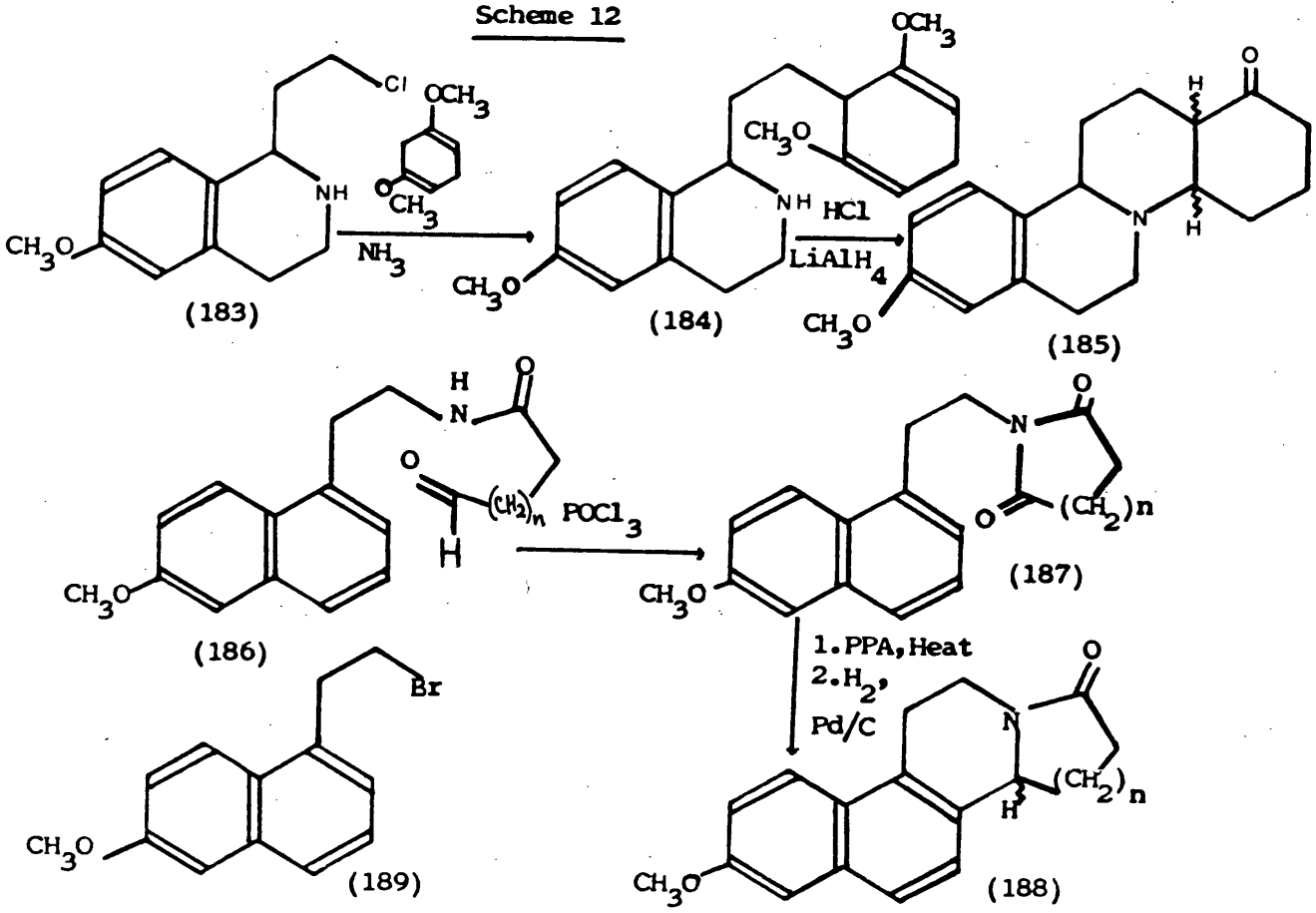
2.3.3.9

Acylation of 1-naphthylamine with 2-carbethoxycyclopentanone at 180° gives (220) (R = H), which on cyclization followed by reduction of the 13-double bond with sodium amalgam affords the 11-azasteroid(221) (R = H).[207] Popp *et al.*[208] acylated 5-aminoisoquinoline(222) with 2-carboxycyclopentanone. The ABD intermediate was converted to the methiodide(223), ring A hydrogenated in the presence of Adam's catalyst,

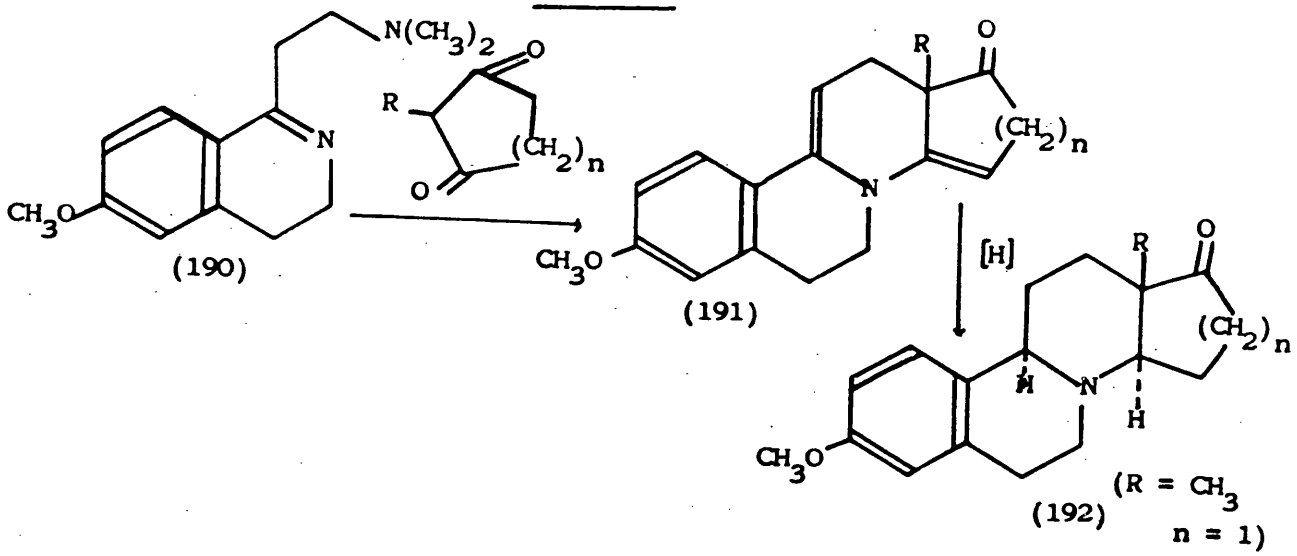
Scheme 11



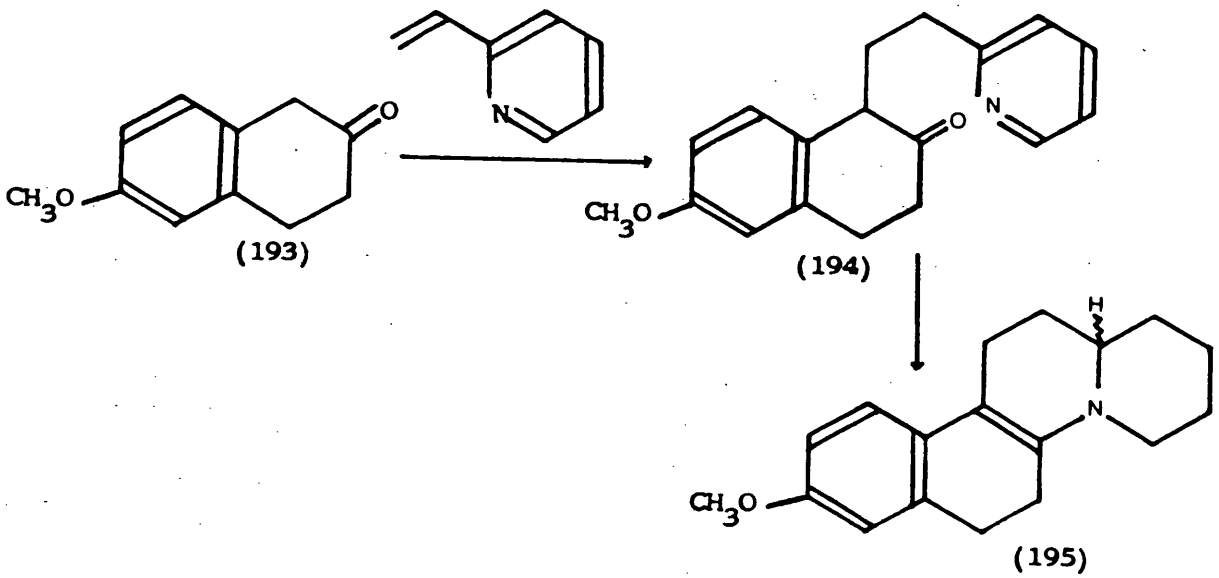
Scheme 12



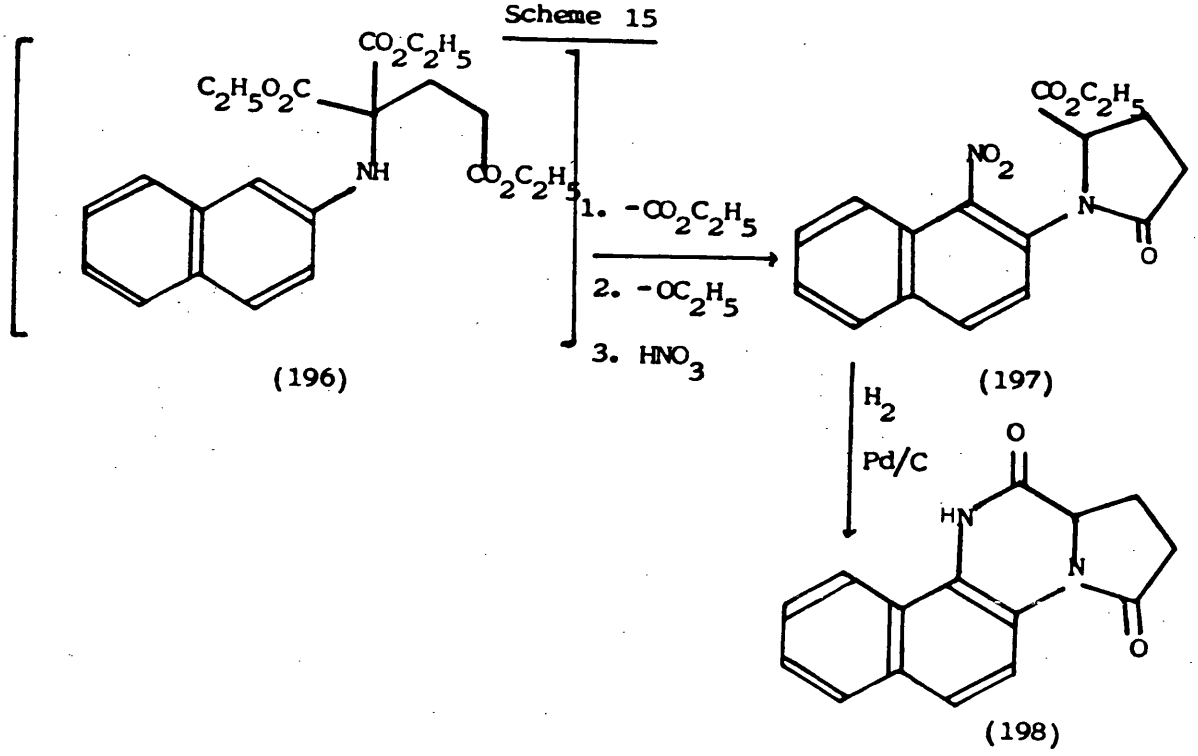
Scheme 13



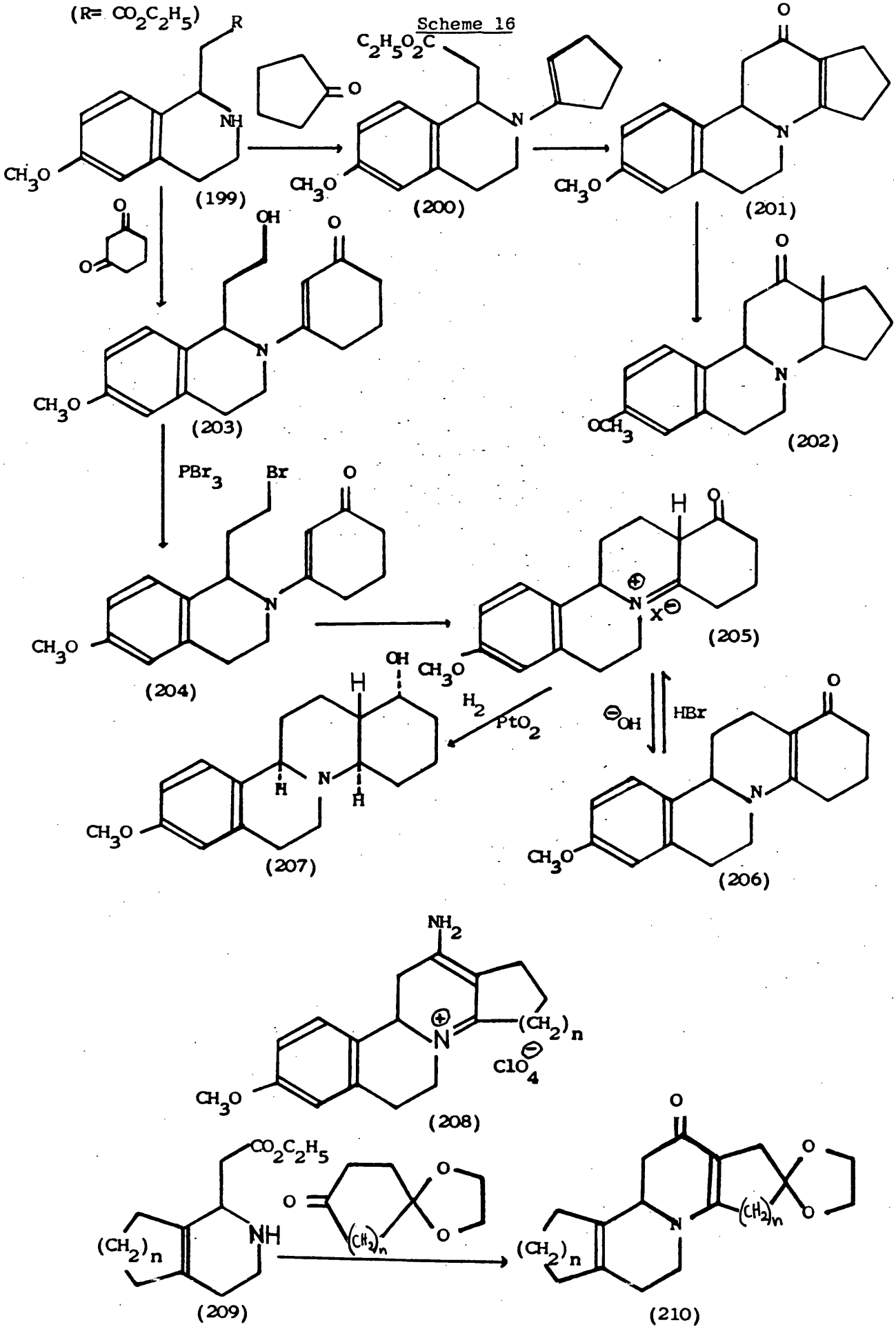
Scheme 14



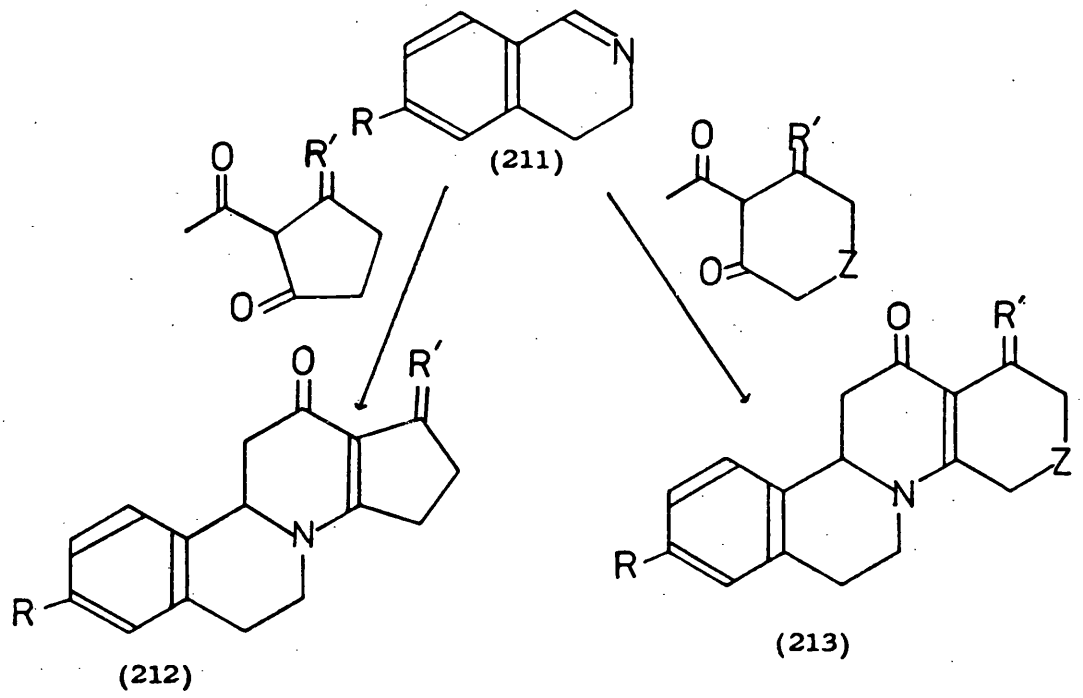
Scheme 15



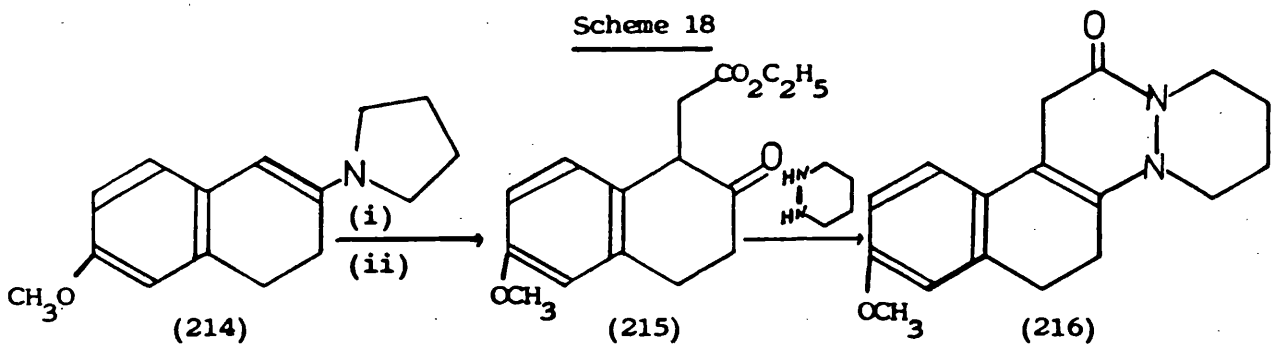
Scheme 16


(R= $CO_2C_2H_5$)
(199)
(200)
(201)
(202)
(203)
(204)
(205)
(206)
(207)
(208)
(209)
(210)
PBr_3
H_2
PtO_2
HBr
CH_3O
OCH_3
$C_2H_5O_2C$
$CO_2C_2H_5$
NH_2
$ClO_4^\ominus$
$X^\ominus$
$(CH_2)_n$

Scheme 17

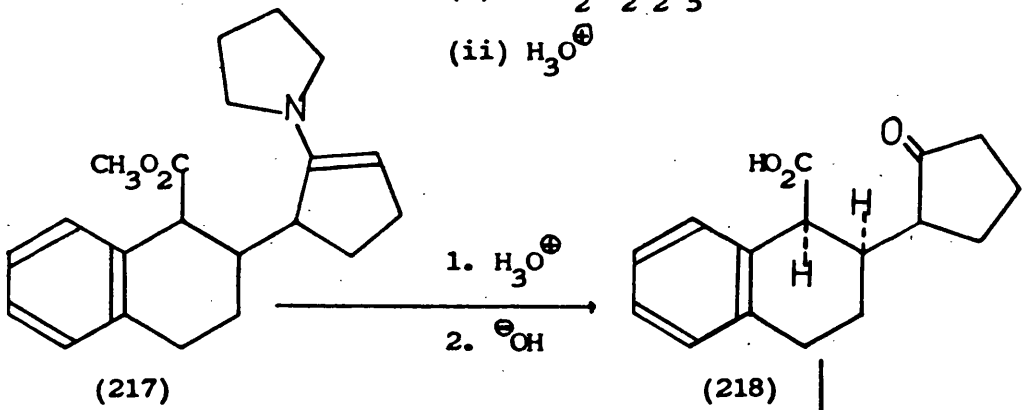


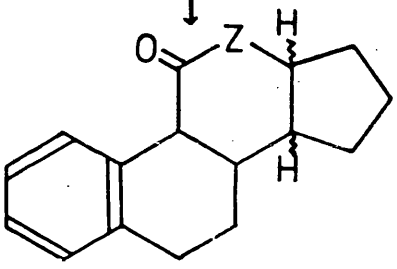
Scheme 18



(i) $BrCH_2CO_2C_2H_5$

(ii) $H_3O^{\oplus}$





and the intermediate was cyclized with polyphosphoric acid to give the 3,11-diazasteroid(224),[208] (see Scheme 19).

2.3.3.10

The ABD intermediates(225) (n = 1,2) have been prepared from the Grignard intermediate(228) and cyclopentanone or cyclohexanone respectively, which on standing in solutions of dimethyl azidodiformate gave (226).[209,210] The latter can be hydrolytically decarboxylated by heating with hydrazine hydrate, and the products oxidized to the 11,12-diazasteroids(227) (n = 1,2) (see Scheme 20).

2.3.3.11

Schiff bases(230) (see Scheme 21), have been prepared from α-naphthylamines(229) and 2-formyl- or 2-acetyl-1,3-cyclohexanedione, which cyclized in the presence of polyphosphoric acid to give the 11-azasteroids(231).[211,212,113] Phenylhydrazones(233) of 6-methoxytetralone(232) can cyclize in refluxing ethanolic hydrochloric acid to give the 11-aza-C-nor-D-homosteroids(234). The 6,11-diaza analogues have been prepared in a similar manner.[214]

2.3.3.12

Bertin and Perronnet[215] report the synthesis of 10-azasteroids.[216]

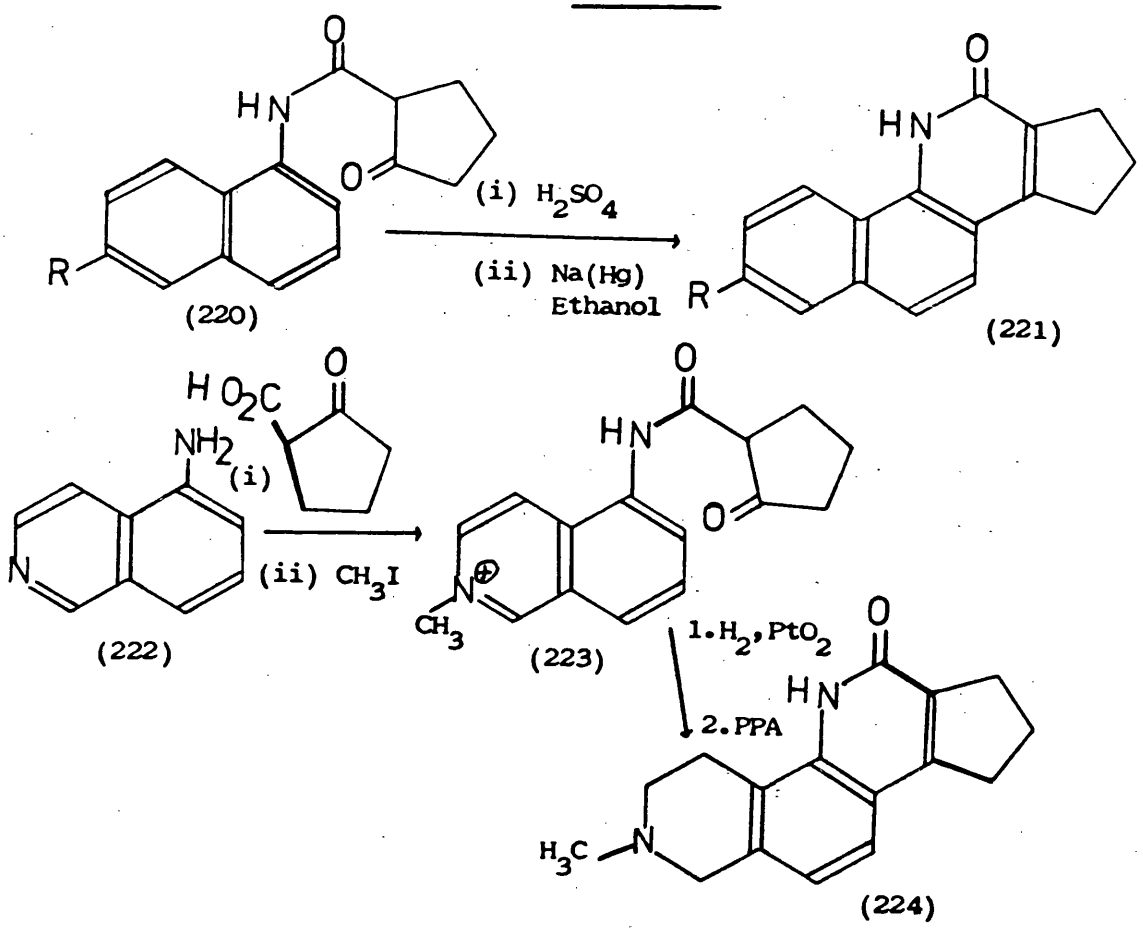
2.3.3.13

Artús et al. have attempted the synthesis of 4,6-diazasteroids.[217] Scheme 22 portrays a unique reaction sequence leading to a 5,10-diazasteroid.[218] Pandit and Huisman[154] have reviewed the synthesis of heterocyclic steroids via enamines and dienamines. 6,7-Diazasteroids have been prepared[219,220,221] via CD enamine intermediates (see Scheme 23).

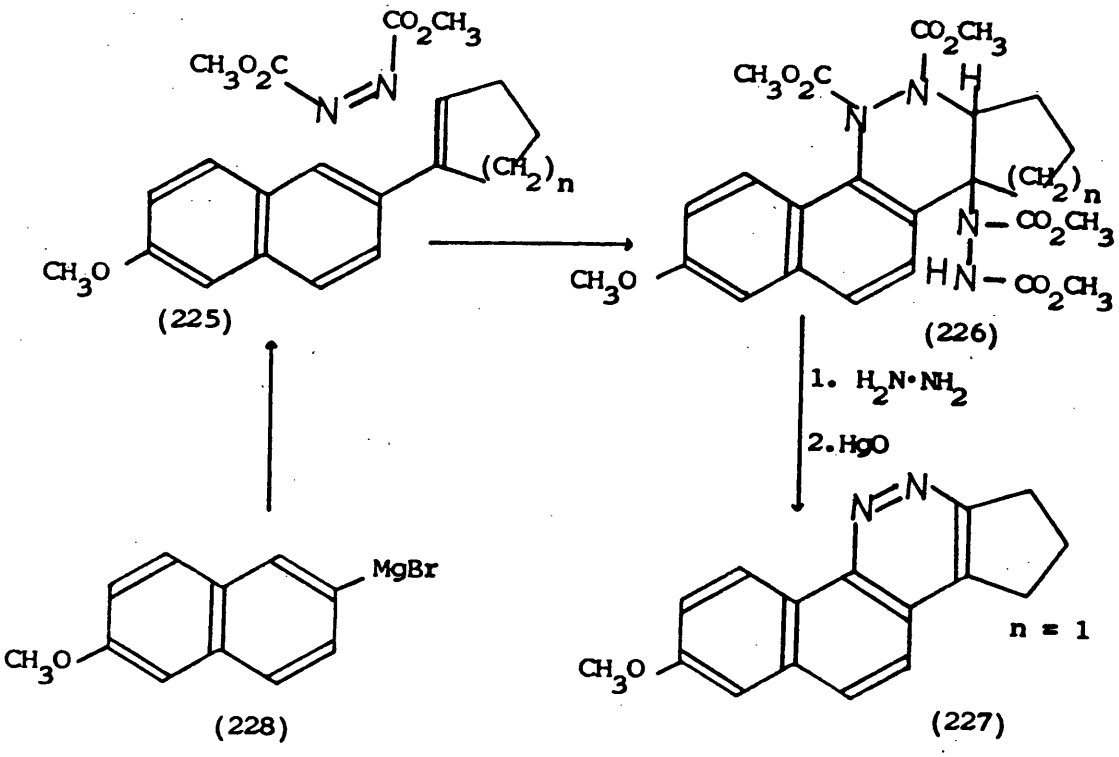
The synthesis of 2,3-dimethoxy-8,11-diazagona-1,3,5(10),9(11)-tetraene has been reported by Castle et al.[222]

8,13-Diazasteroids can be obtained via the AD intermediate(250)[223,224] (see Scheme 24). Under normal Bischler-Napieralski reaction conditions, the intermediate (250) can be cyclized to the dihydroisoquinoline(256).[225, 226] Acid hydrolysis followed by catalytic hydrogenation furnished the

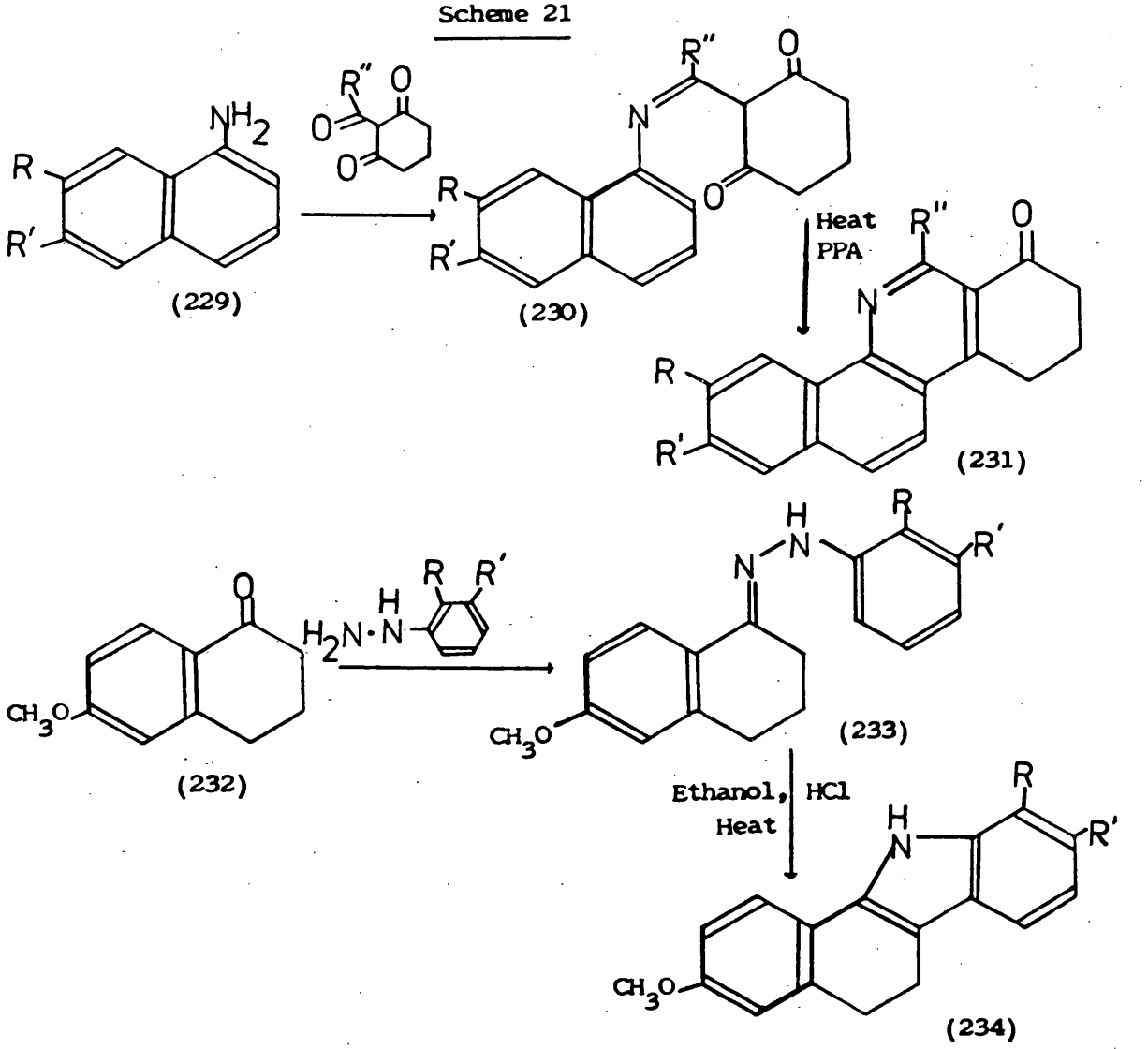
Scheme 19



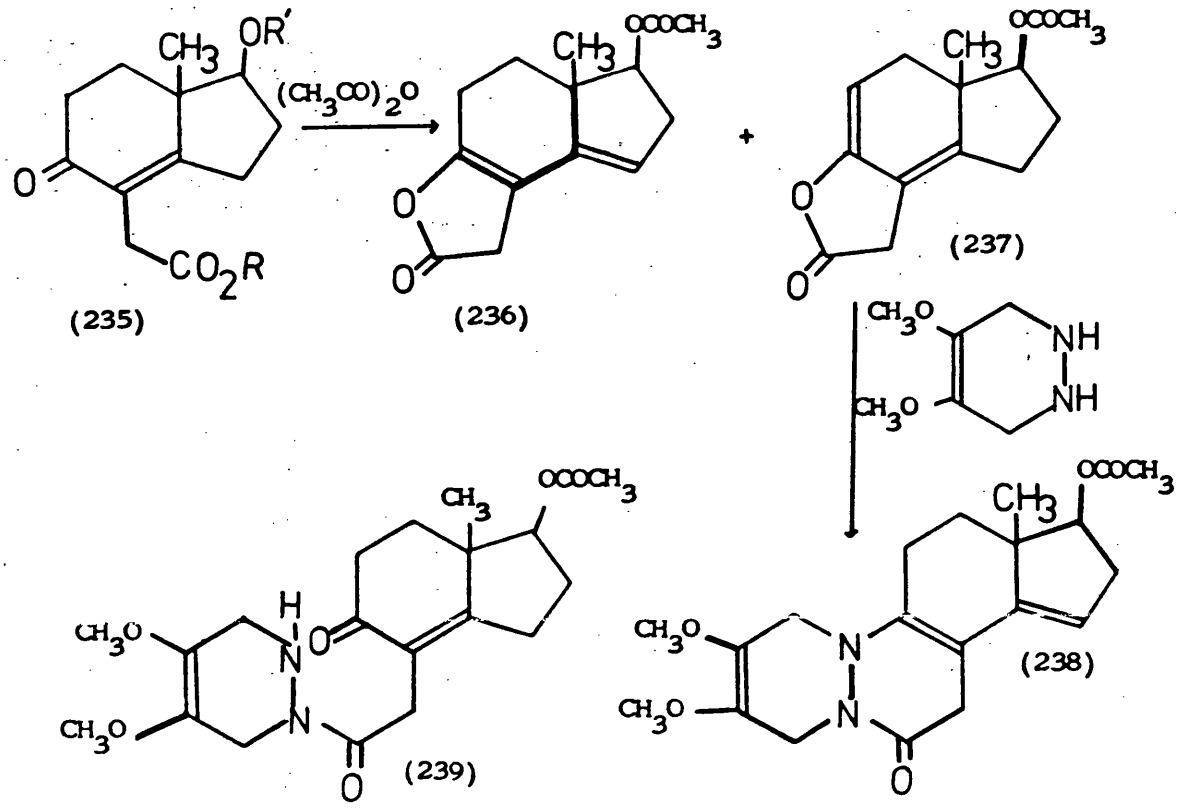
Scheme 20



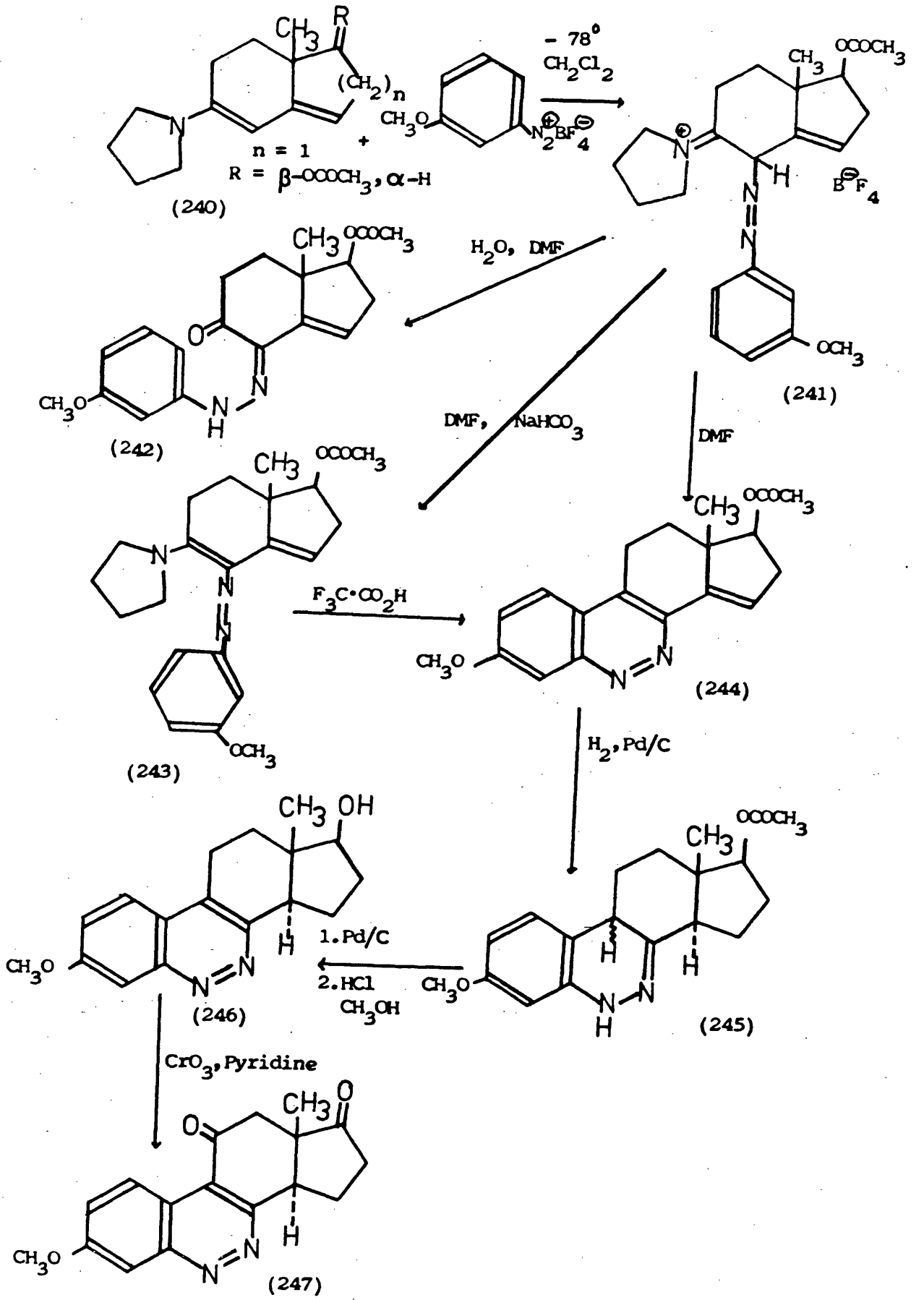
Scheme 21



Scheme 22



Scheme 23


n = 1
R = β-OCOCH3, α-H
(240)
- 78°
CH2Cl2
(241)
H2O, DMF
(242)
DMF, NaHCO3
DMF
(243)
F3C·CO2H
(244)
H2, Pd/C
(245)
1. Pd/C
2. HCl
CH3OH
(246)
CrO3, Pyridine
(247)

diamine(255) (R = R' = OMe; R = OMe, R' = H), which underwent condensation with ethyl 3-ethoxycarbonylpropionimidate hydrochloride[225] to give 8(14)-dehydro-(257). The diazasteroid(257) can be obtained directly from (256) via a reductive cyclization procedure.[224,226]

2.3.4 Some recent advances in the field of azasteroid synthesis

The four isomeric 3,11-diamino-5α pregnanes(258) have been prepared by Campbell et al.[227] The same group[228] also report the synthesis of eight, isomeric, steroidal vicinal 2,3-amino alcohols(259). The seven possible 3-amino-2-hydroxy and 2-amino-3-hydroxy isomers of the anti-arrhythmic steroid[229] 3α-amino-2β-hydroxy-5α-androstan-17-one(259) (2-OH, 3-NH_2) have been prepared from 5α-androst-2-en-17-one.

Several new steroidal heterocycles have been synthesised by Sykes et al.,[230] including androst-4-eno[3,2-f]-(s-triazolo[4,3-b] pyridazine)(260); the androstano[17,16-f]-(s-triazolo[4,3-b]pyridazines) (261) and (262); and, 3-methoxyoestra-1,3,5(10)-trieno[17,16-f]-(s-triazolo[4,3-b]pyridazine)(263). Azasteroids (264), (265), (266), (267), and (268) have also been prepared by Sykes and Bajwa.[231]

Junjappa et al.[232] report the synthesis of naphthonaphthyridine derivatives (269) which may be broadly speaking, considered as aza-steroids. They[233] also report the synthesis of novel substituted and fused pyrazolo[4,3-c]pyridone and pyrido[4,3-d]pyrimidine derivatives, such as (270)[234] and (271).[233]

Omar and Ashour[235] have synthesised some novel steroidal hydrazones containing quinazoline moieties.

Electrochemical cyclization has afforded compounds of type (272).[236]

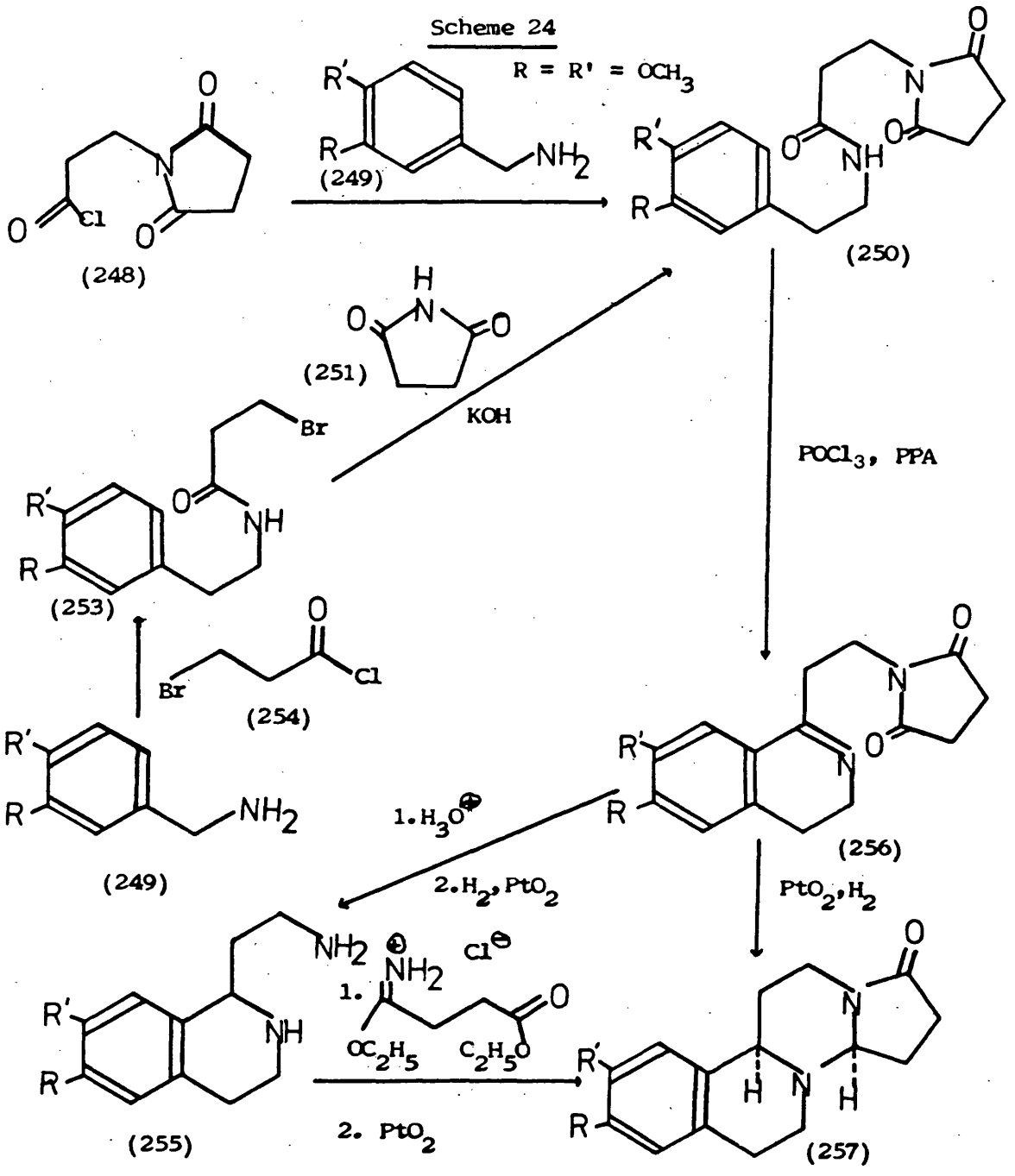
Several polyazadithiasteroidal analogues have been prepared by Fravolini et al.[237] (see Figure 6). The synthesis of thiadiazasteroid analogues (see Figure 7), has also been reported.[238]

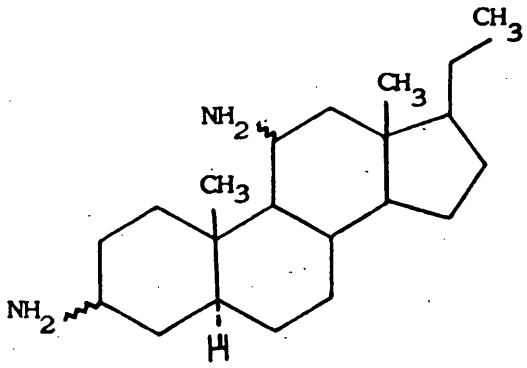
Bridgehead nitrogen heterocycles, including the 8,13-diazasteroids (283) have been prepared by Scovill and Burckhalter.[239]

Lalezari et al.[240] report the synthesis of several interesting polyazasteroids (see Figure 8).

Steroidal aziridines(287) have been prepared by Ghaffari and Ghaffari.[241]

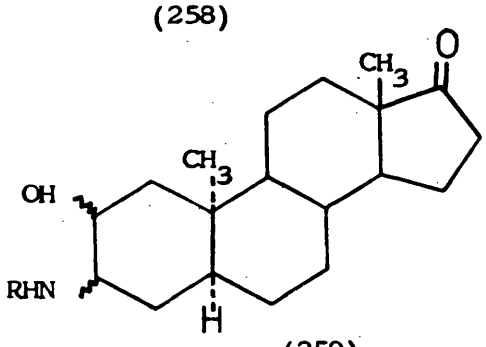
Scheme 24


R = R' = OCH3
(248)
(249)
(250)
(251)
KOH
POCl3, PPA
(253)
(254)
(249)
1. H3O⊕
2. H2, PtO2
(256)
PtO2, H2
(255)
1.
2. PtO2
(257)

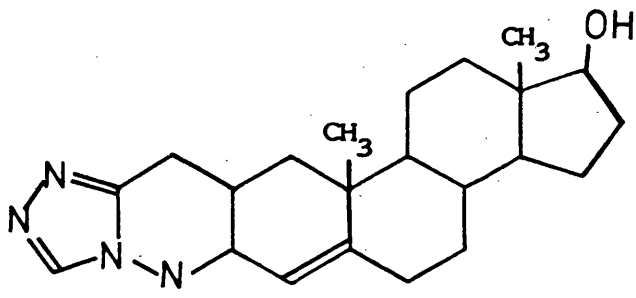


(i) 3β, 11α
(ii) 3α, 11α
(iii) 3β, 11β
(iv) 3α, 11β

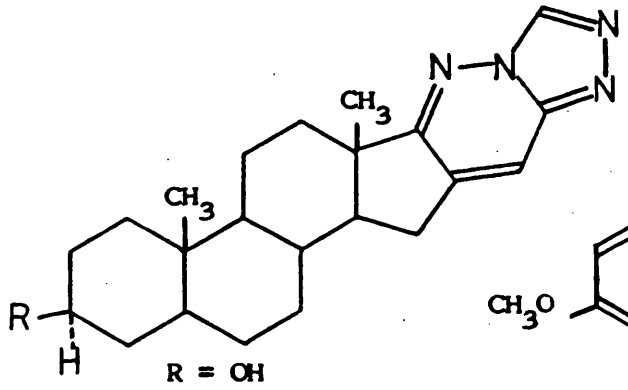
(258)



(259)



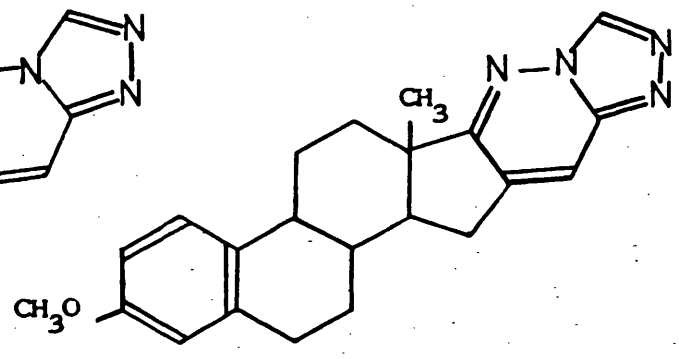
(260)



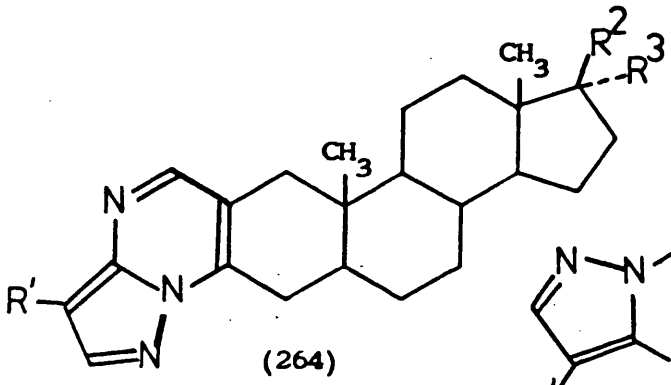
R = OH

(261) (R=OH).

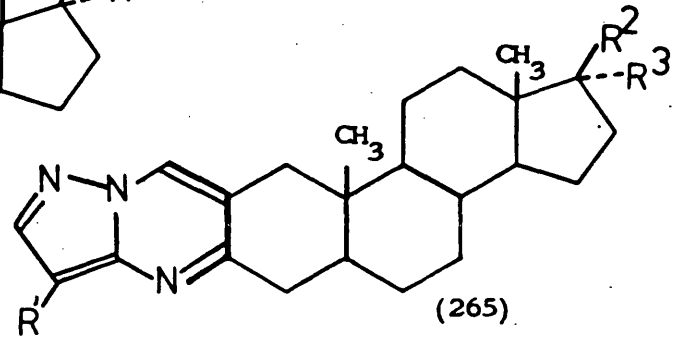
(262) (R=OH, Δ^5).



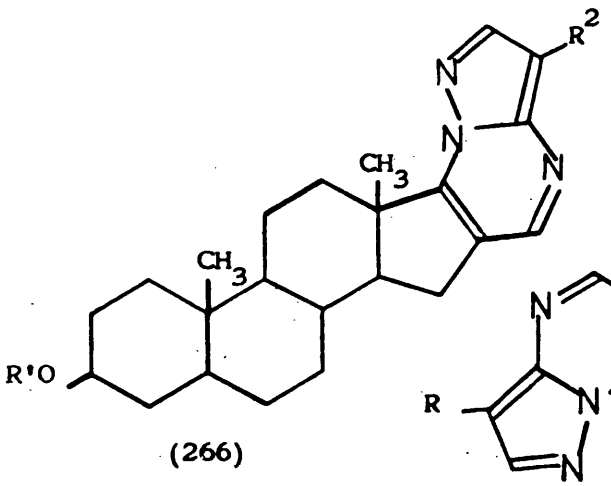
(263)



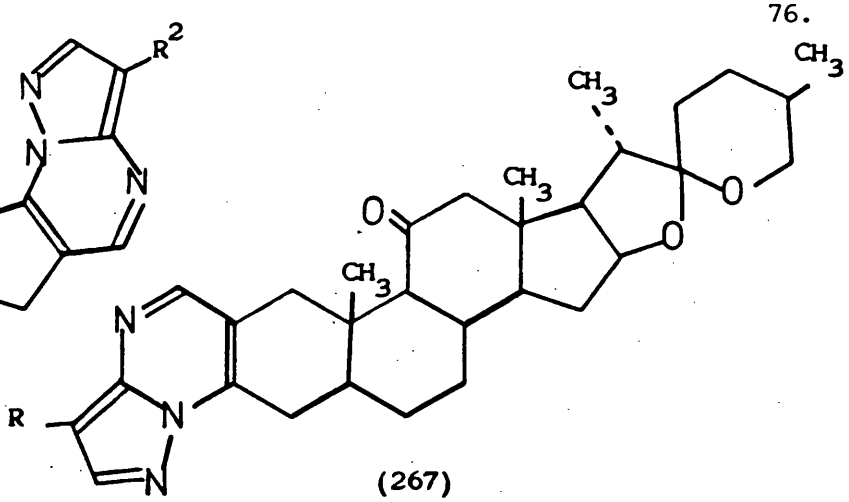
(264)



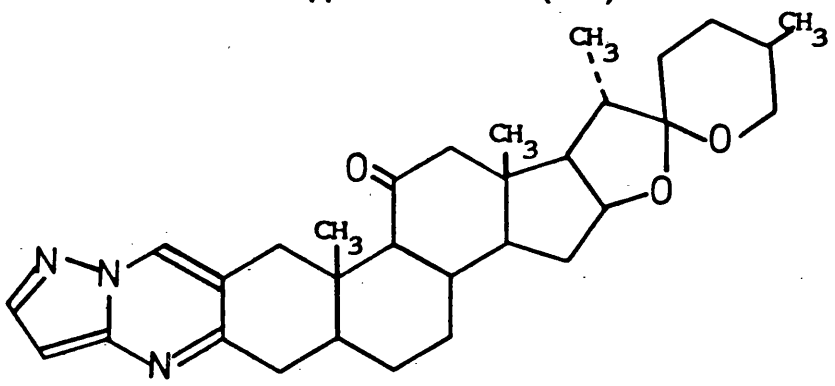
(265)



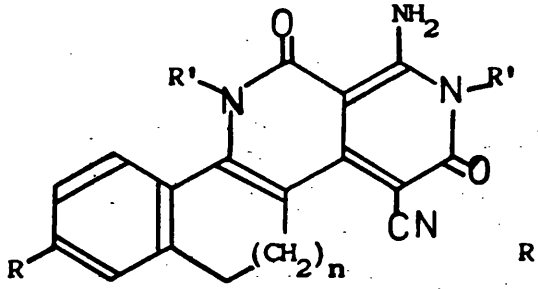
(266)



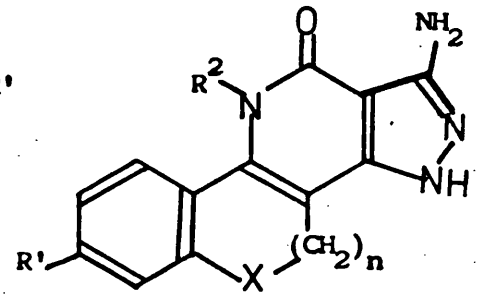
(267)



(268)

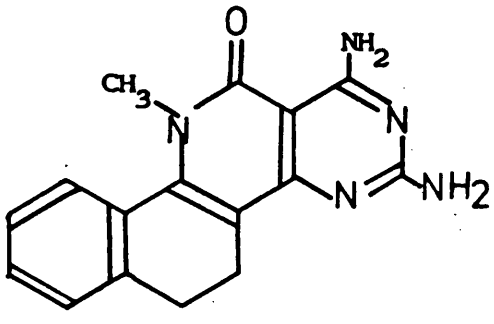


(269)

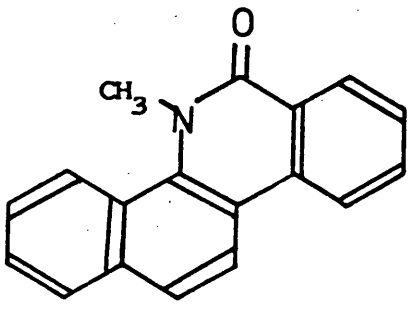


(270)

(X = C ,S ,O)

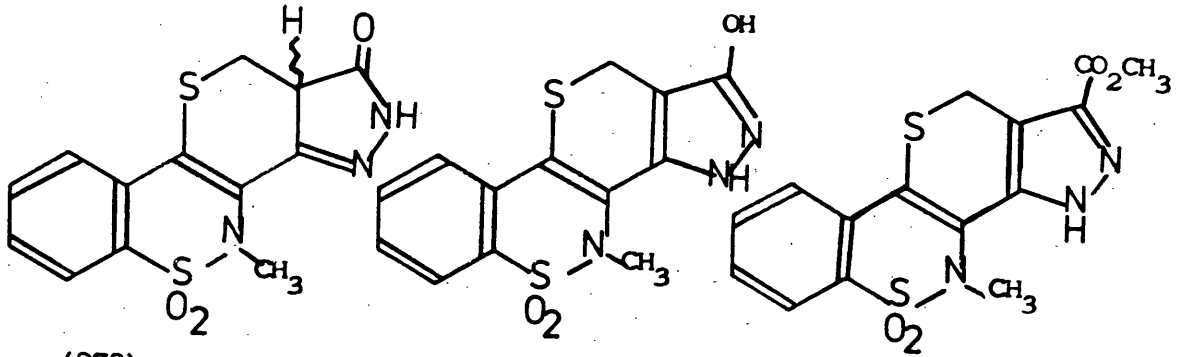


(271)



(272)

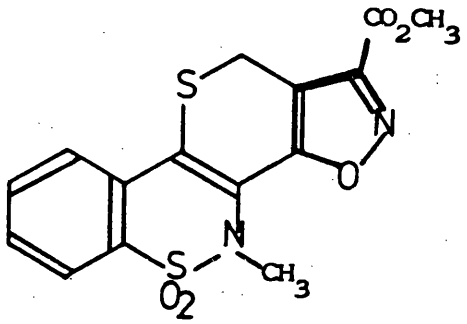
Figure 6



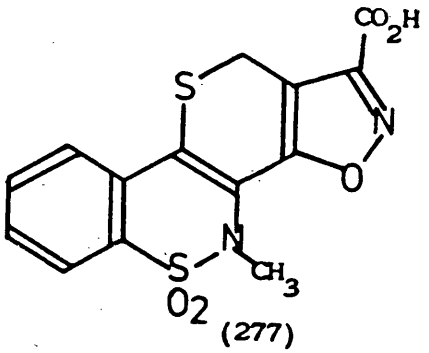
(273)

(274)

(275)

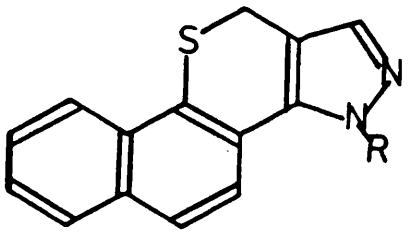


(276)



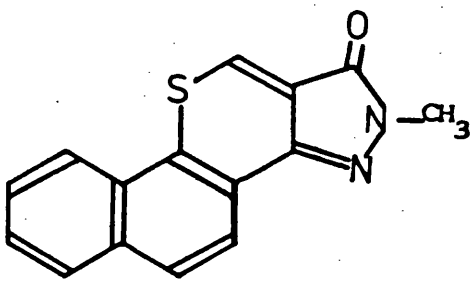
(277)

Figure 7

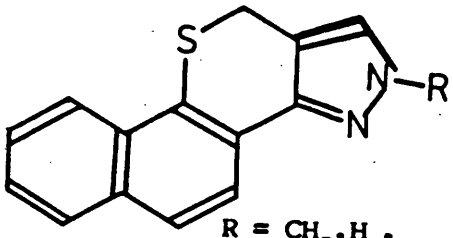


R = CH_3 ; C_6H_5

(278)

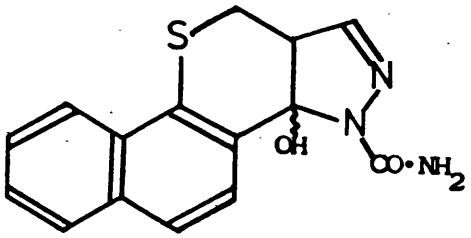


(279)

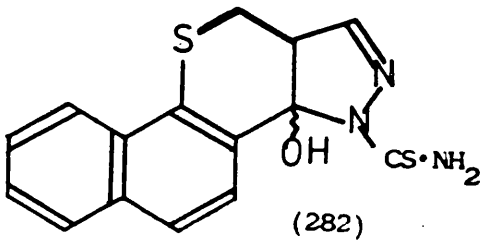


R = CH_3, H , $COCH_3$

(280)



(281)



(282)

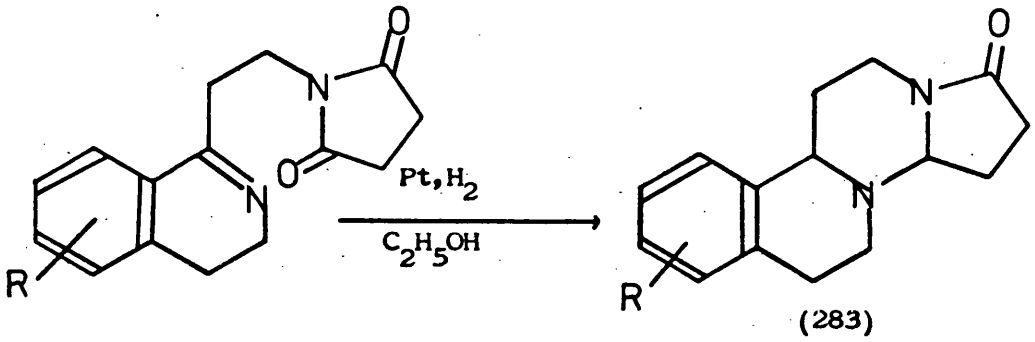
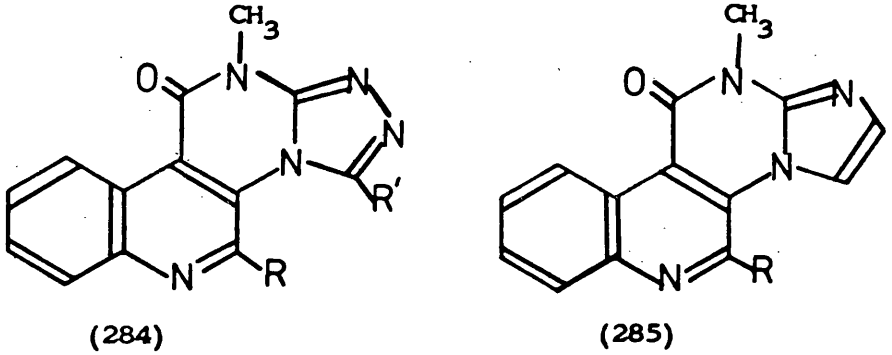
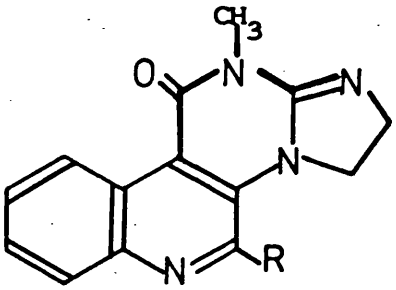

O
N
O
Pt, H_2
C_2H_5OH
R
(283)

Figure 8


CH_3
O
N
R'
R
(284)
(285)


CH_3
O
N
R
(286)

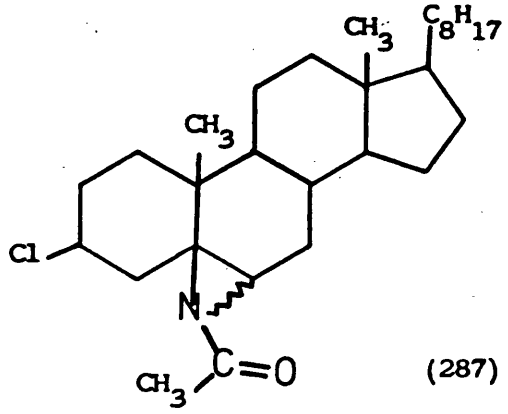
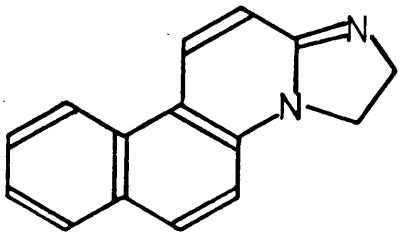
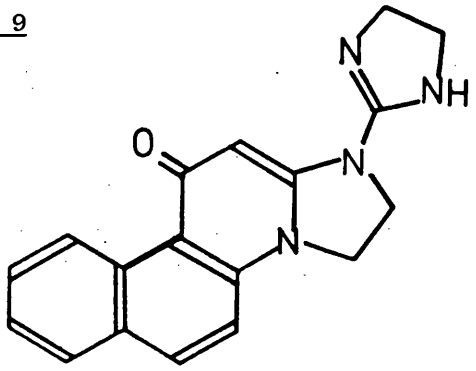

CH_3
C_8H_{17}
CH_3
Cl
N
C=O
CH_3
(287)

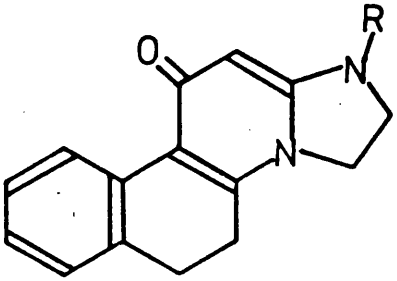
Figure 9



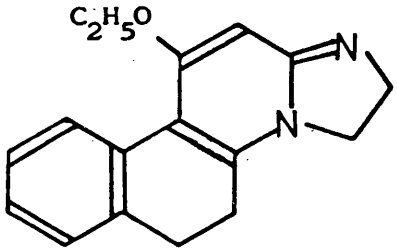
(288)



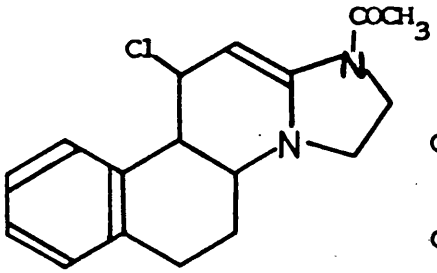
(289)



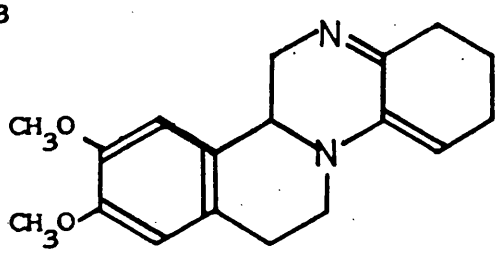
(290)



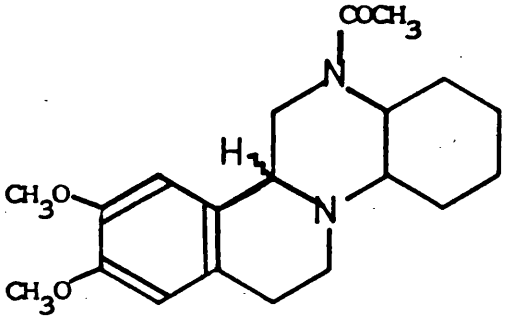
(291)



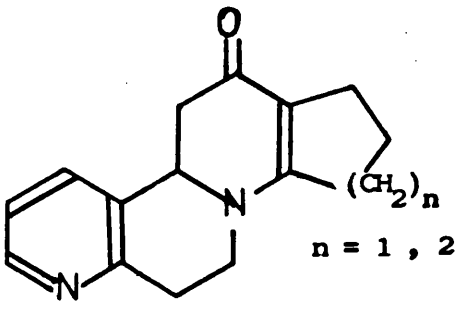
(292)



(293)



(294)



n = 1 , 2

(295)

Yamazaki et al. report the successful preparation of 14,17-diazasteroids[242] (288), (289), (290), (291), and (292); 8,12-diaza-D-homosteroids[243] (293) and (294); and the 4,8-diazasteroids[244](295) (see Figure 9).

2.4 Azasteroids - Activity in the central nervous system and other biological responses

The broad spectrum of biological activity displayed by the steroids generally together with the multiplicity of action exhibited by certain individual members, make the steroids one of the most intriguing classes of biologically active compounds. The altered physical and chemical properties of azasteroids are envisaged to lead to the discovery of new, potentially useful drugs.

The azasteroids examined to date have been shown to possess one or more of the following activities:- (i) adrenocortical; (ii) anti-mineralocortical; (iii) anabolic; (iv) androgen antagonistic; (v) biosynthetic inhibitor; (vi) oestrogenic/anti-oestrogenic; (vii) progestative/anti-progestative; (viii) anti-fertility; (ix) catatoxic; (x) cardiac; (xi) anti-lipemic; (xii) CNS-acting; (xiii) neuromuscular blocking; (xiv) local anaesthetic; (xv) antimicrobial; and, (xvi) anti-neoplastic.

The reader is referred to the excellent review by Singh, Kapoor and Paul[245] for further details. However, some of the pharmacological activities of azasteroids are summarised in Table 5.

The pharmacological activities of some naturally occurring, nitrogen containing steroidal molecules has been reviewed in 1962 by Martin-Smith et al.[257] Martin-Smith et al.[258,259] have also reviewed the biological activity present in derivatives of naturally occurring steroids possessing nitrogen atoms.

Structure-activity relationships and stereochemical factors influencing biological activity of azasteroids are discussed in some detail by Bush.[267]

Table 5

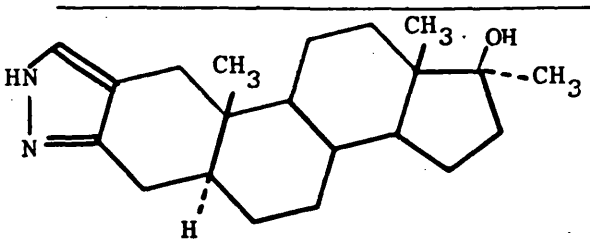
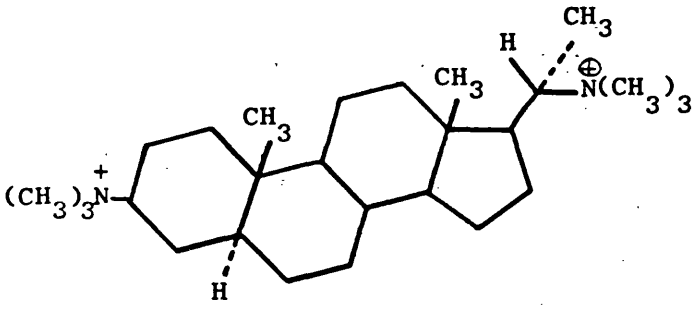
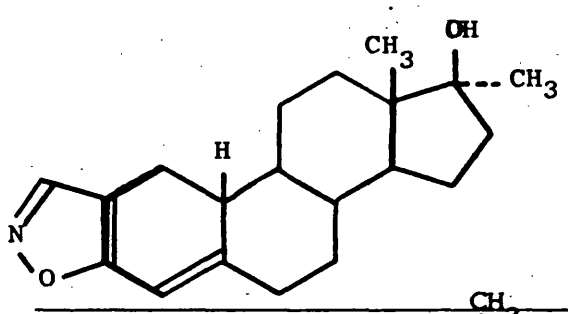
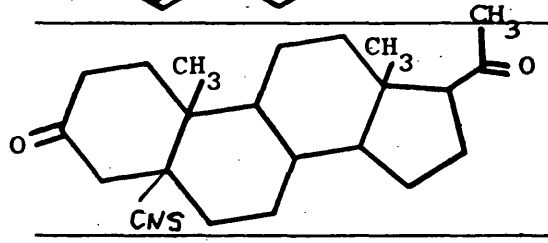
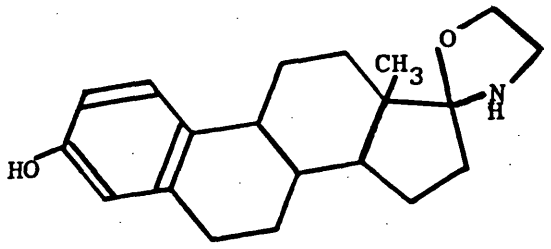
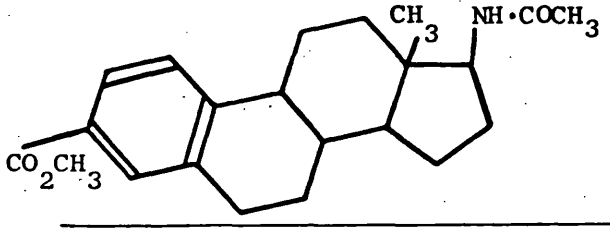
Structure	Activity	Reference
	17β-Hydroxy-17α-methylandrost-ano-[3,2-c]-pyrazole. Anabolic activity.	246,247
	Naturally occurring bisquat-ernary steroidal alkaloid-malquetine. Neuromuscular-blocking potency equivalent to that of (+)-tubocurarine, but having a lower toxicity.	248
	17β-Hydroxy-17α-methyl-19-norandrost-4-eno-[2,3-d]-isoxazole. Progestational activity equal to that of progesterone; also anabolic, androgenic and oestrogenic properties.	246,249
	3,20-Dioxo-5α-thiocyanato-pregnane. Progestational activity.	250,251
	17-Spiro-oxazolidine derivative of oestrone. Oestrogenic activity ten times greater than that of oestrone.	252
	17β-Acetamido-3-acetoxy-oestra-1,3,5(10)-triene. Potent oestrogenic activity.	253

Table 5 (Continued)

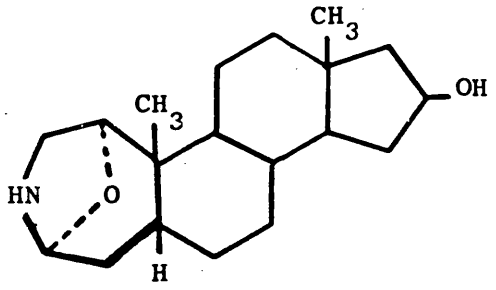
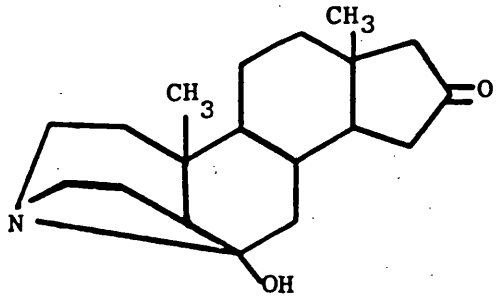
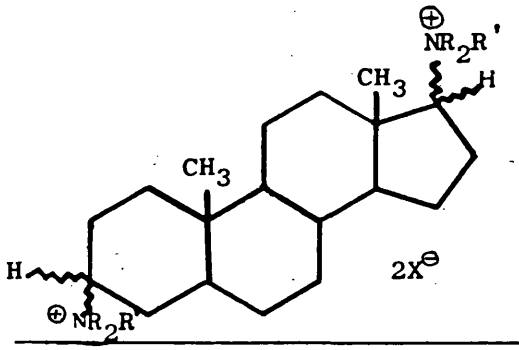
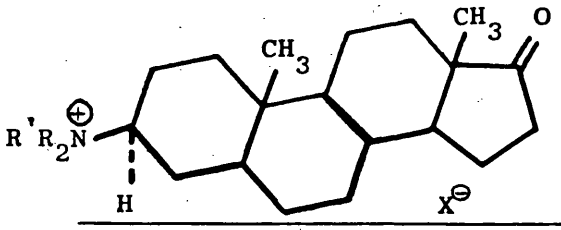
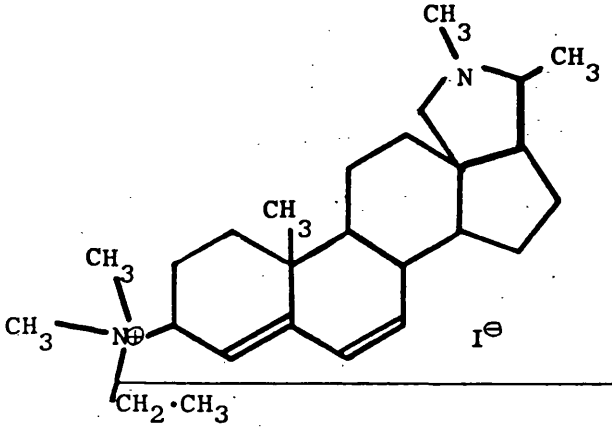
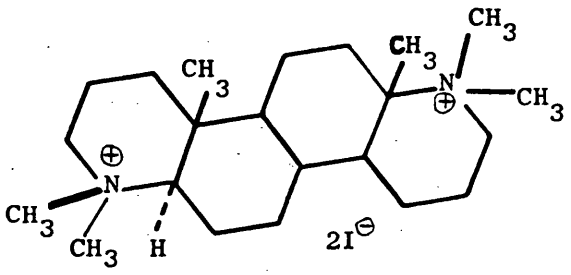
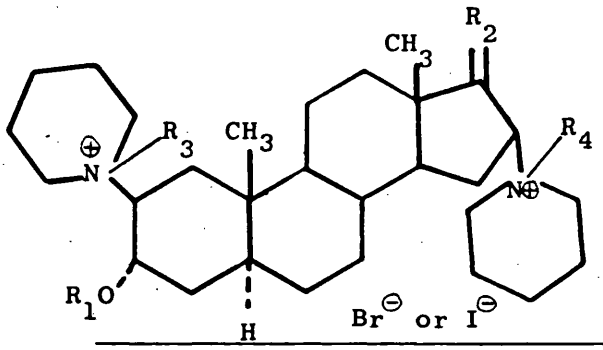
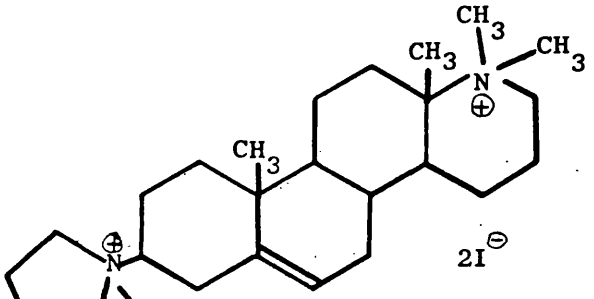
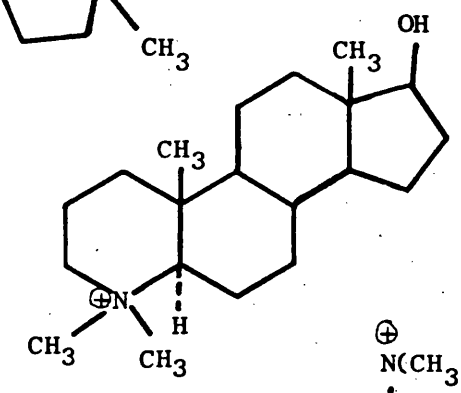
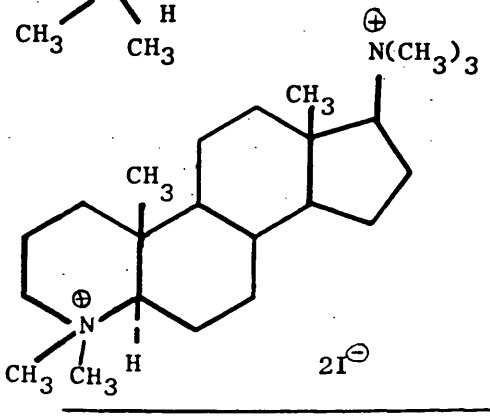
Structure	Activity	Reference
	Samandarine-salamander alkaloid. Analeptic activity, producing convulsions and antagonising the narcotic effects of barbiturates.	254,255, 256
	Cycloneosamandione-salamander alkaloid Analeptic activity, producing convulsions and antagonising the narcotic effects of barbiturates.	254,255, 256
	Salts of 5α-androstane derivatives Selective interaction with nucleic acids	260
	" "	260
	Stercuronium iodide. Neuromuscular blocking agent.	261,268

Table 5 (Continued)

Structure	Activity	Reference
	4,17a-Dimethyl-4,17a-diaza-D-homo-5α-androstane dimethiodide and other 4,17a-diaza-D-homo-steroids. Neuromuscular blocking agents.	262,265, 266
$Br^{\ominus}$ or $I^{\ominus}$ 	Pancuronium bromide(Pavulon) (R_1 = Ac; R_2 = β-OAc, H; R_3 = CH_3; R_4 = CH_3), and other steroidal structures containing acetylcholine fragments. Neuromuscular blocking agents.	263,269
	Mono and bisquaternary aza steroids. Neuromuscular blocking, ganglion blocking and vagolytic activity.	264,266
$I^{\ominus}$ 	" "	"
	" "	"

CHAPTER THREE

REVIEW OF ISOQUINOLINES

3.1 History

For many centuries, the dried latex exuded from the seed capsule of the opium poppy, Papaver somniferum, has been employed to alleviate pain and also to induce a state of euphoria when injested. The euphoric and analgesic agent, morphine, was the first nitrogenous base to be isolated from living organisms, in 1805. The structure of morphine[364] was elucidated in 1925, when it was found to be a member of the alkaloids based on the isoquinoline nucleus.[271]

Considerable interest in the synthesis of isoquinoline derivatives[500] has developed owing to the frequent occurrence of the isoquinoline nucleus in alkaloids.

3.1.1

Some recently isolated isoquinoline alkaloids are illustrated in Table 6.

3.2 Synthesis

Three of the many methods developed for the synthesis of isoquinolines are:-

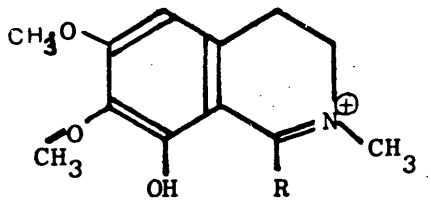
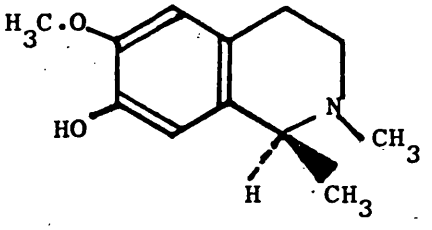
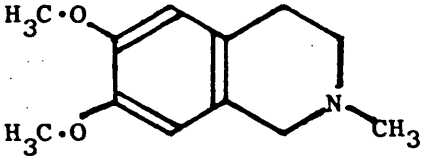
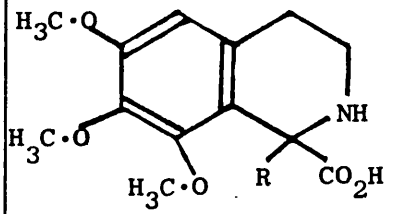
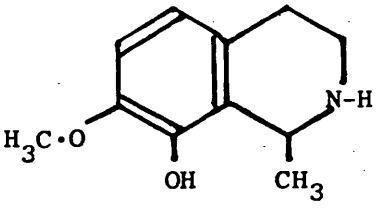
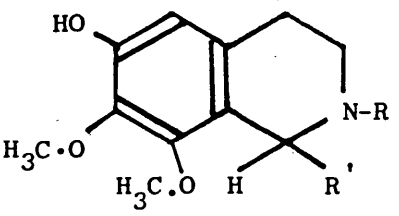
(a) Bischler-Napieralski,

(b) Pictet-Spengler, and

(c) Pomeranz-Fritsch.

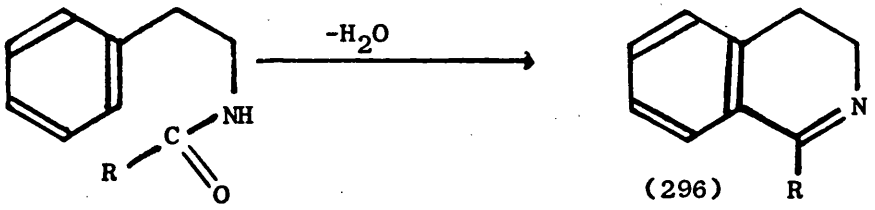
Table 6

Simple Isoquinoline Alkaloids

Trivial Name	Structure	Reference
Anhalotine; R = H Peyotine; R = CH_3		287,286
(+)-1-Methylcorypalline		288
O-Methylcorypalline		289
O-Methylpeyoxylic acid; R = H O-Methylpeyoruvic acid; R = CH_3		290
Arizonine		
Isoanhalamine; R = H, R' = H Isoanhalidine; R = CH_3, R' = H Isoanhalonidine; R = H, R' = CH_3 Isopellotine; R = CH_3, R' = CH_3		291,286

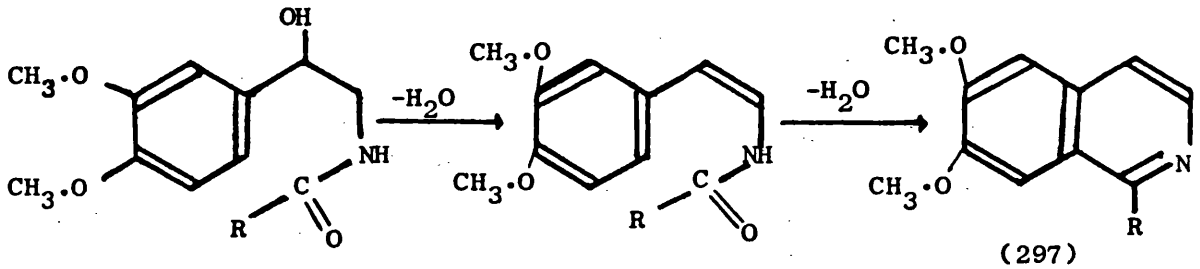
3.2.1

3,4-Dihydroisoquinolines(296) were first prepared by Bischler and Napieralski[272] by cyclodehydration of β-phenethylamides.

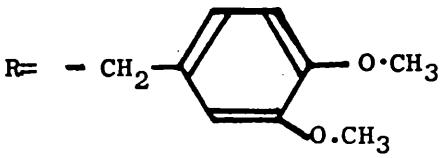


(296)

Modification of the reaction by Pictet and Gams,[273-4] in which the isoquinoline is obtained directly from β-hydroxy-β-phenethylamide, resulted in improved yields, as shown in the classical synthesis of papaverine(297).[274]



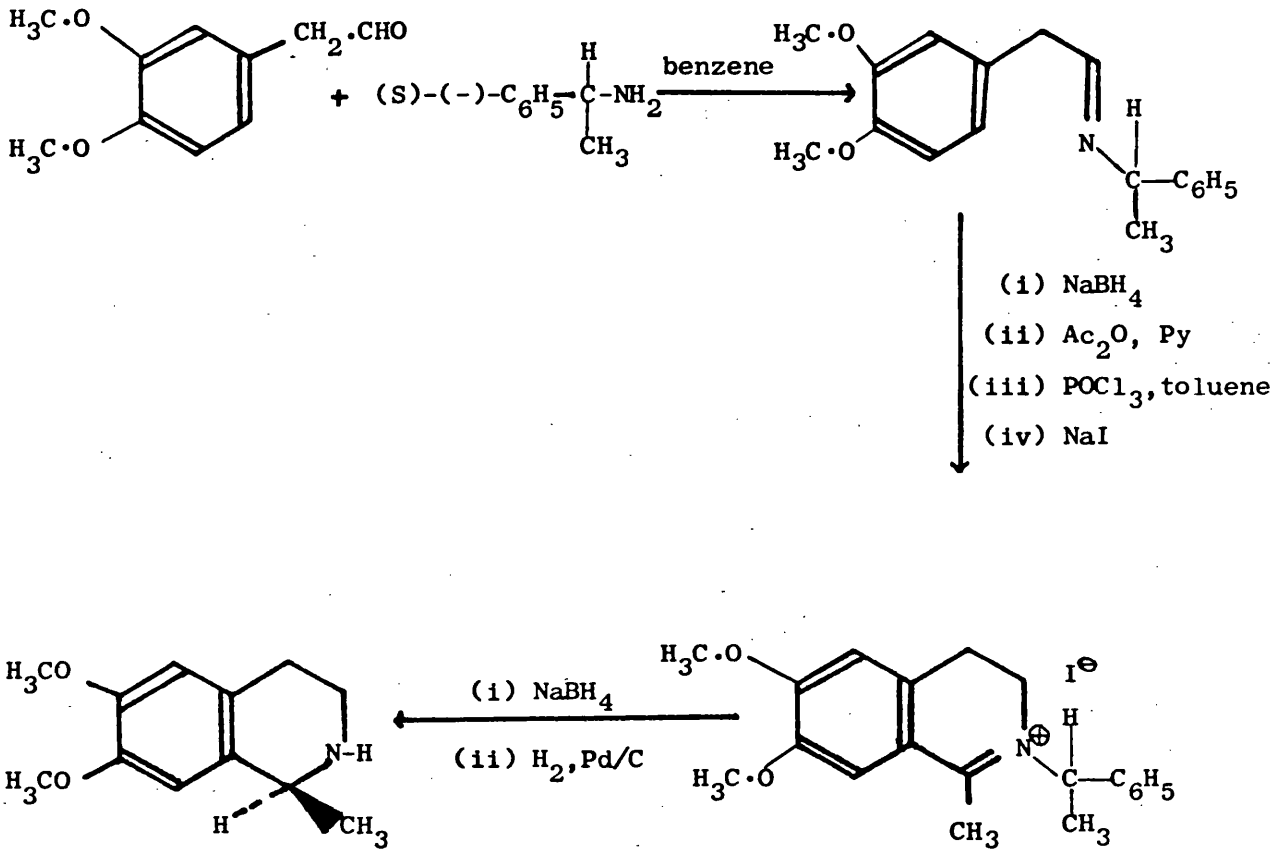
(297)



Numerous methods of synthesizing isoquinoline derivatives have been reviewed by Bergstrom[275] and Manske.[276] The Bischler-Napieralski reaction is discussed in depth by Whaley et al.[277]

Optically pure Salsolidines can be prepared by the Bischler-Napieralski route, using optically active immonium salts [292-3] (see Scheme 25).

Scheme 25

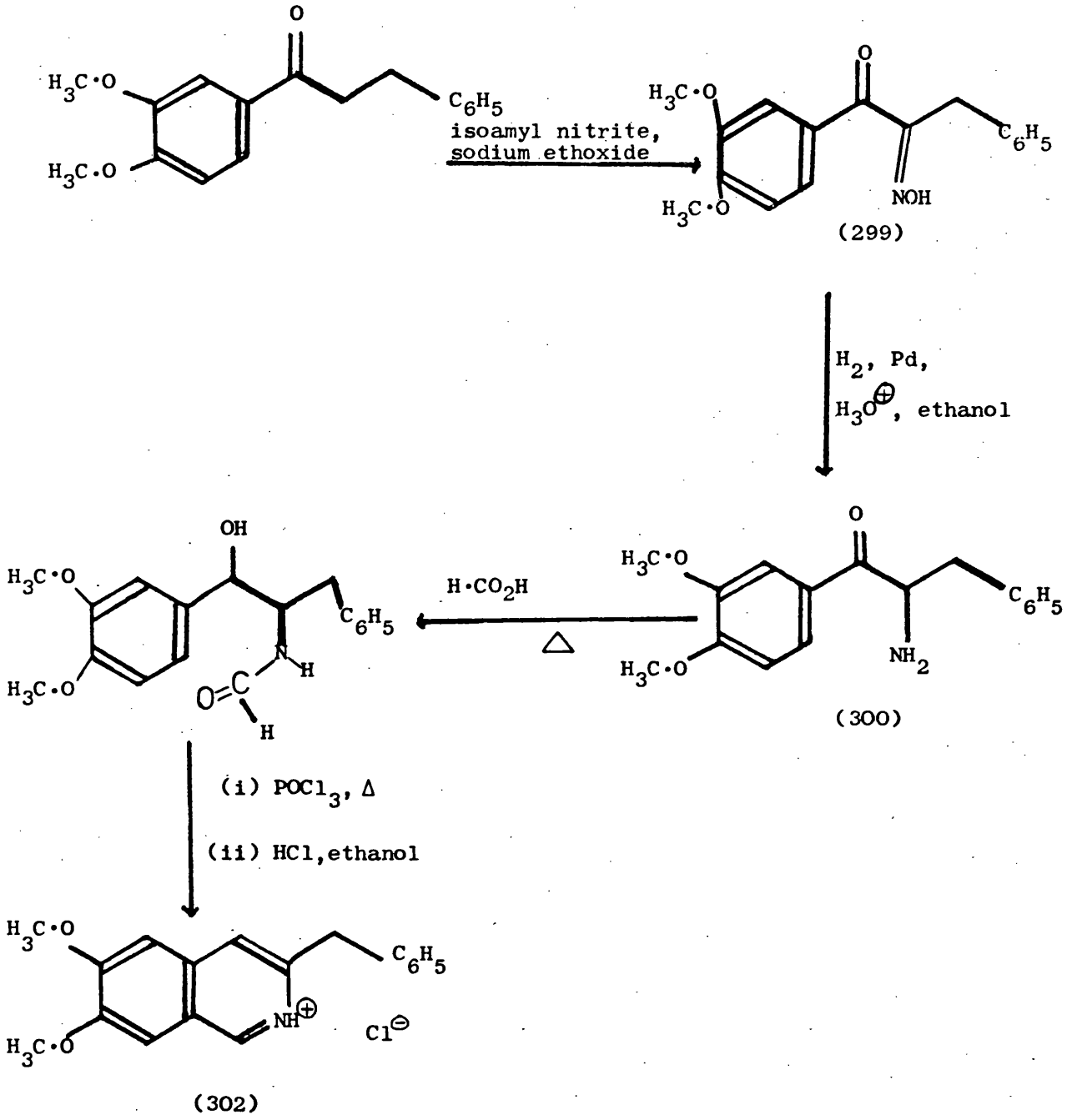


(-)-Salsolidine

(298)

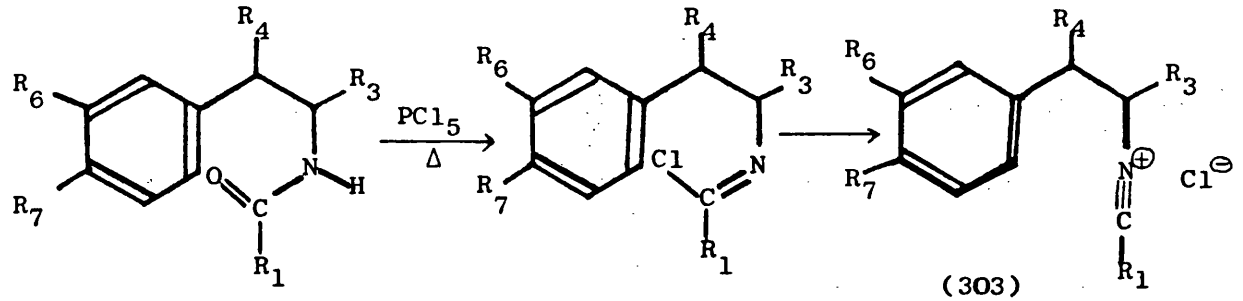
In a novel variation of the Bischler-Napieralski approach, ω-phenylisonitrosopropiophenone(299) is reduced to an amino alcohol, followed by N-formylation and cyclization, resulting in the formation of a 3-benzylisoquinoline derivative(302)[294] (see Scheme 26).

Scheme 26

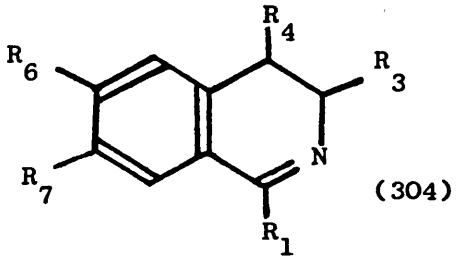


3.2.1.1 Mechanism

Fodor et al.[295] have shown that nitrilium cations(303) are intermediates in the Bischler-Napieralski cyclization whenever secondary amides are used. A nitrilium ion was trapped as its crystalline hexafluoroantimonate salt.[296]



(303)

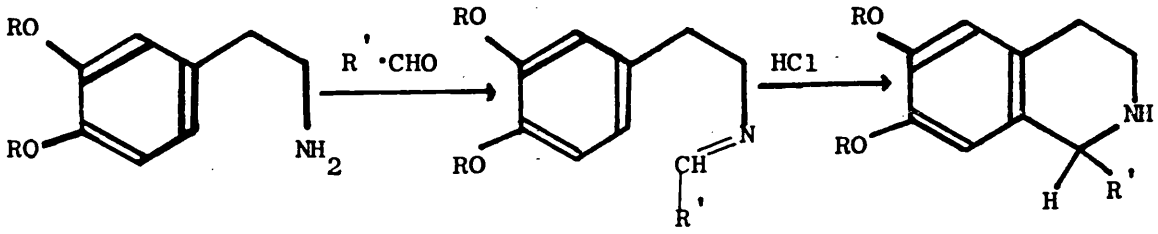


(304)

3.2.2

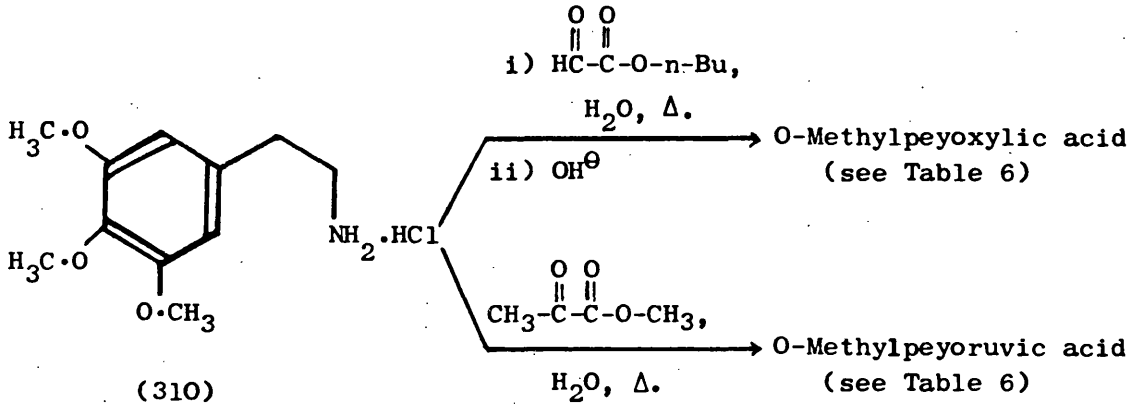
The Pictet-Spengler* reaction[278] involves the condensation of β-arylethylamine with a carbonyl compound to yield a tetrahydroisoquinoline, and may be considered to be a special example of the Mannich reaction.[279] The reaction* was extended by Decker[280] to the condensation of substituted phenethylamines with various aldehydes (see Scheme 27). For further details of this reaction*, the reader is referred to the review by Whaley et al.[277]

Scheme 27



A variety of optically active tetrahydroisoquinolines have been prepared by this route, some of which are shown in Scheme 28.[297-300]

The Pictet-Spengler cyclization has also been employed to prepare the alkaloids O-methylpeyoxylic and O-methylpeyoruvic acids from mescaline hydrochloride(310).[290]



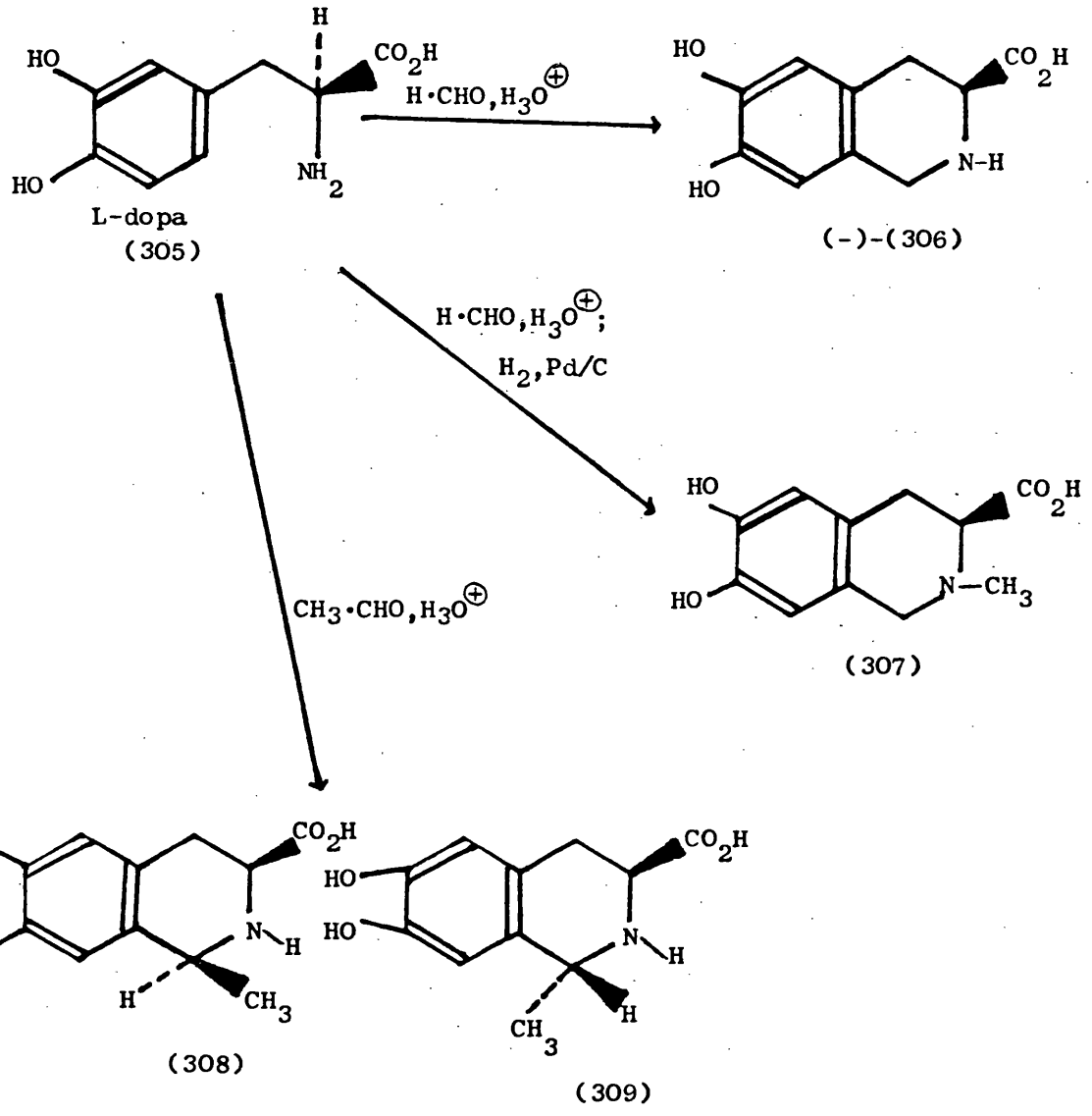
(310)

A study of the synthesis of tetrahydroisoquinolines *via* the cyclization of Schiff bases under neutral[303] or weakly acidic conditions has been carried out. As expected, a phenolic group *ortho* or *para* to the cyclization site greatly facilitates the reaction.[301,302]

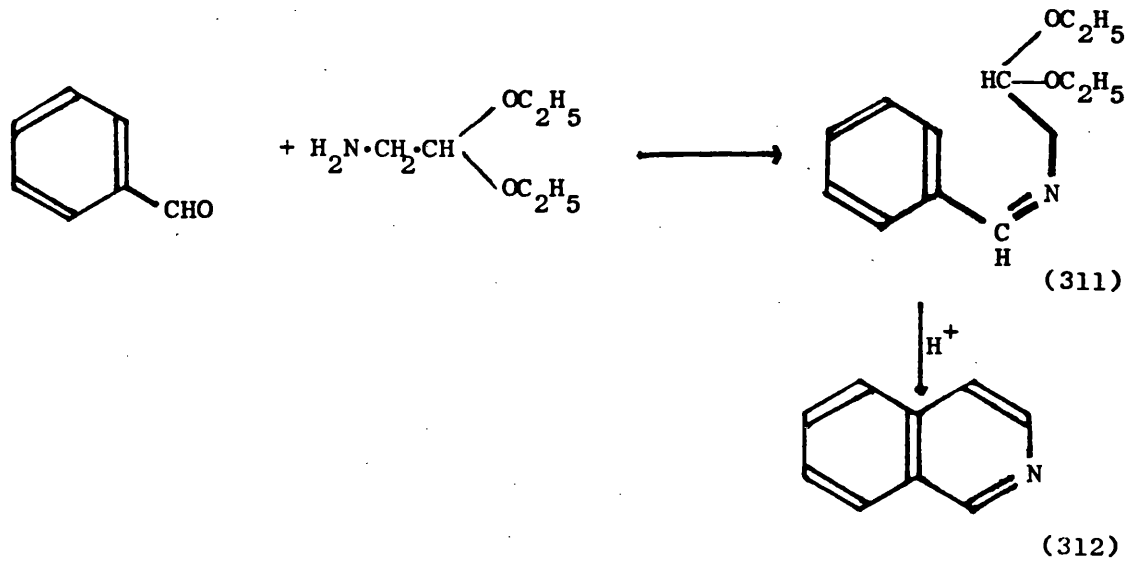
3.2.3

Acid-catalysed cyclization of benzalamino-acetal(311) resulting in the formation of the isoquinoline nucleus(312) was first reported by Pomeranz[281-3] and Fritsch.[284-5] It has since been utilized in the synthesis of a variety of isoquinolines (see Scheme 29). The reaction is discussed in greater detail by Whaley *et al.*[277]

Scheme 28

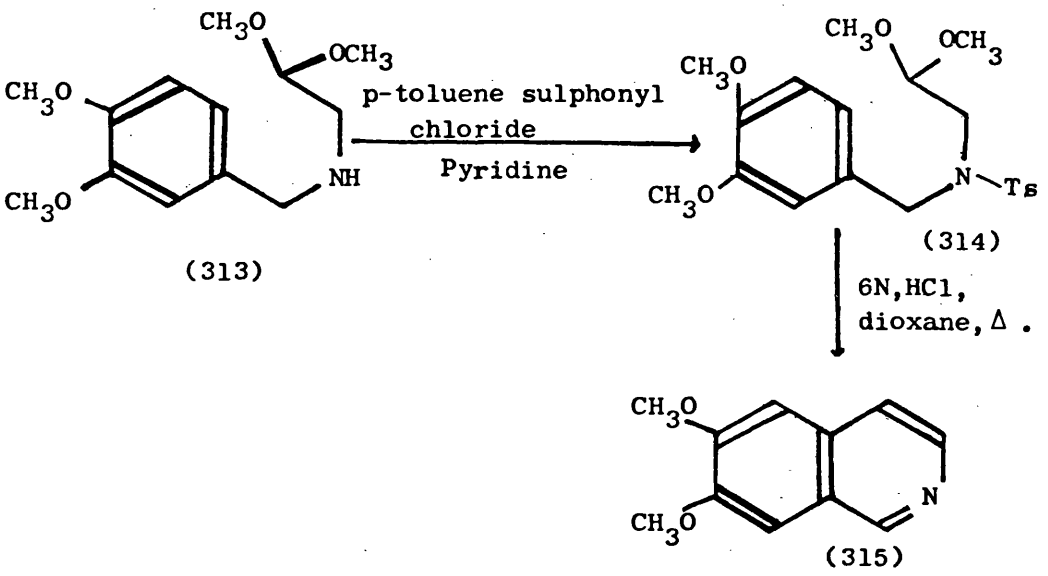


Scheme 29



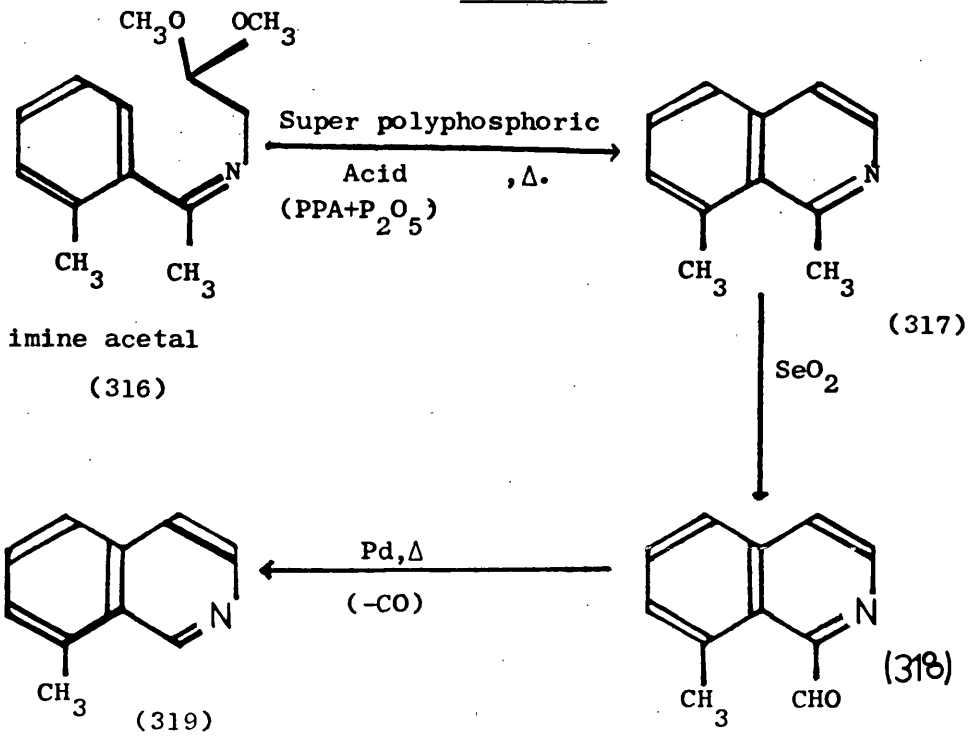
The Pomeranz-Fritsch cyclization, modified[304,316] by Bobbitt to obtain 4-hydroxytetrahydroisoquinolines,[304] continues to be a useful approach.[305-6] Substituted isoquinolines have been prepared by Jackson et al.[307-8] by cyclization of acetal sulphonamides under mildly acidic conditions (see Scheme 30).

Scheme 30

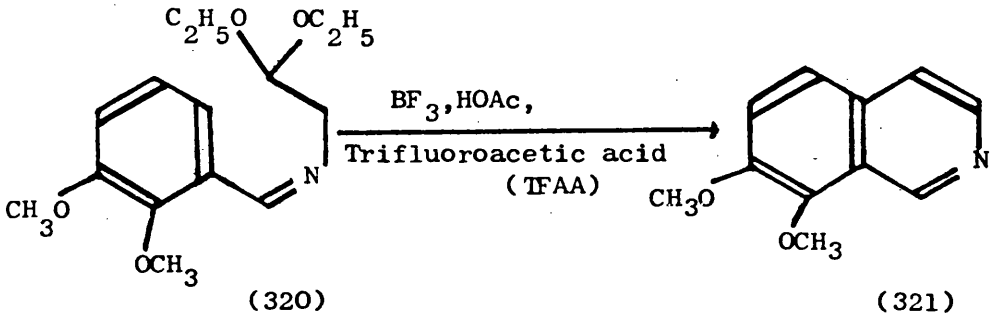


Several other reagents have been successfully employed in the Pomeranz-Fritsch cyclization (see Schemes 31, 32 and 33).

Scheme 31[309]

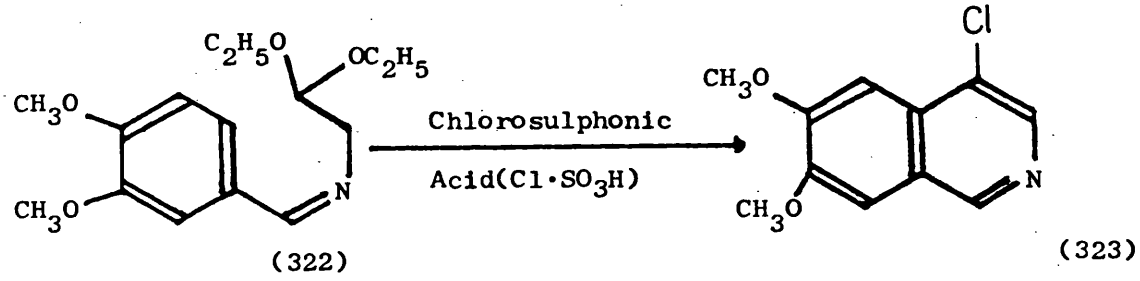


Scheme 32[310,315]



(320) (321)

Scheme 33[311]

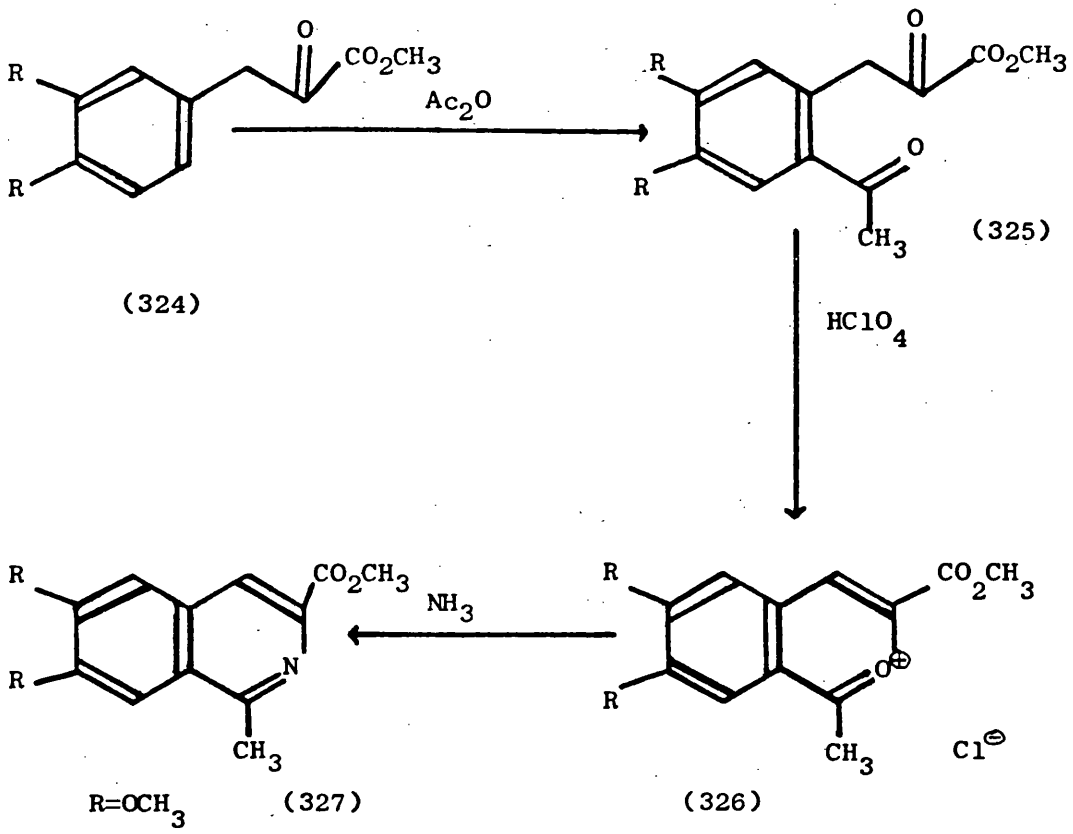


(322) (323)

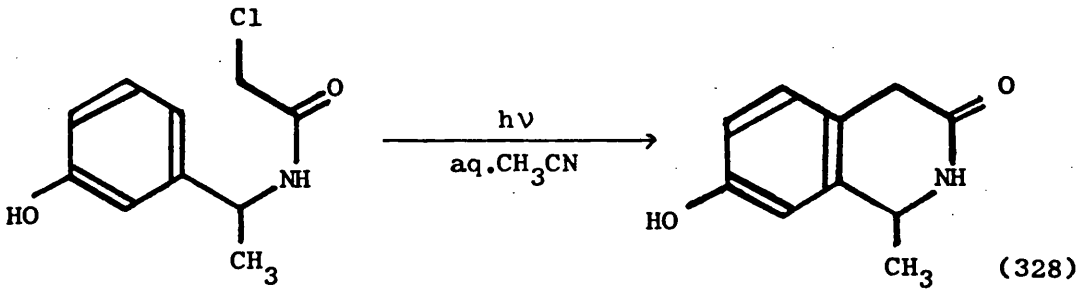
3.2.4 Other synthetic routes leading to isoquinolines

Amination of benzopyrylium salts(326), obtained via acylation of 3,4-dimethoxyphenylpyruvic methyl ester(324) with acetic anhydride followed by acid-catalysed cyclization, also results in the formation of isoquinolines(327) (see Scheme 34).[312]

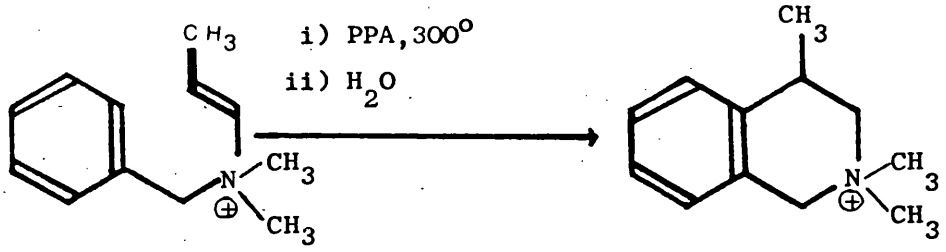
Scheme 34



Ikeda et al.[313] report a novel route to isoquinoline derivatives, involving the irradiation of an N-chloroacetylbenzylamine to give an isoquinoline lactam(328).



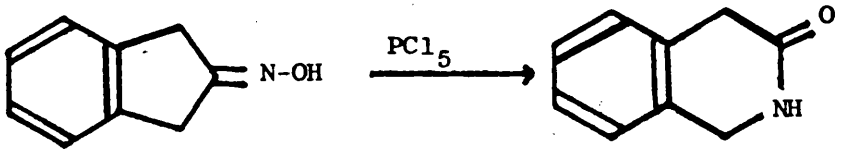
Cyclization of aralkenyl-substituted quaternary ammonium salts in the presence of polyphosphoric acid leads to tetrahydroisoquinoline salts(329).[314]



(329)

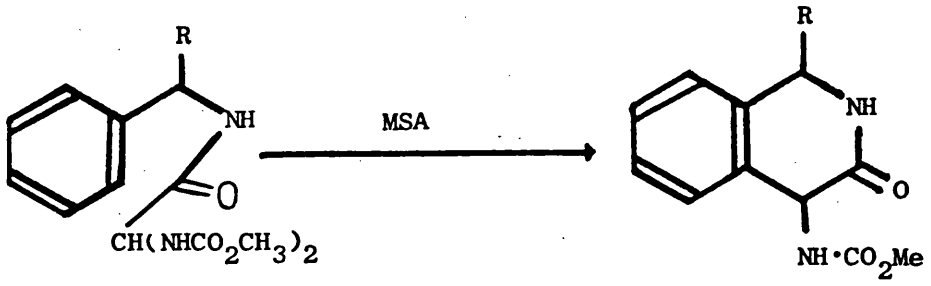
Brossi et al. report[317] a facile synthesis of 1,4-dihydro-isoquinolones and their reduction to the corresponding 1,2,3,4-tetrahydroisoquinolines (see Scheme 35).

An improved synthesis of 1,4-dihydro-3-[2H]-isoquinolone(330) via a Beckmann rearrangement of 2-indanone oxime(331) is reported by Lyle and Walsh.[318]



(331) (330)

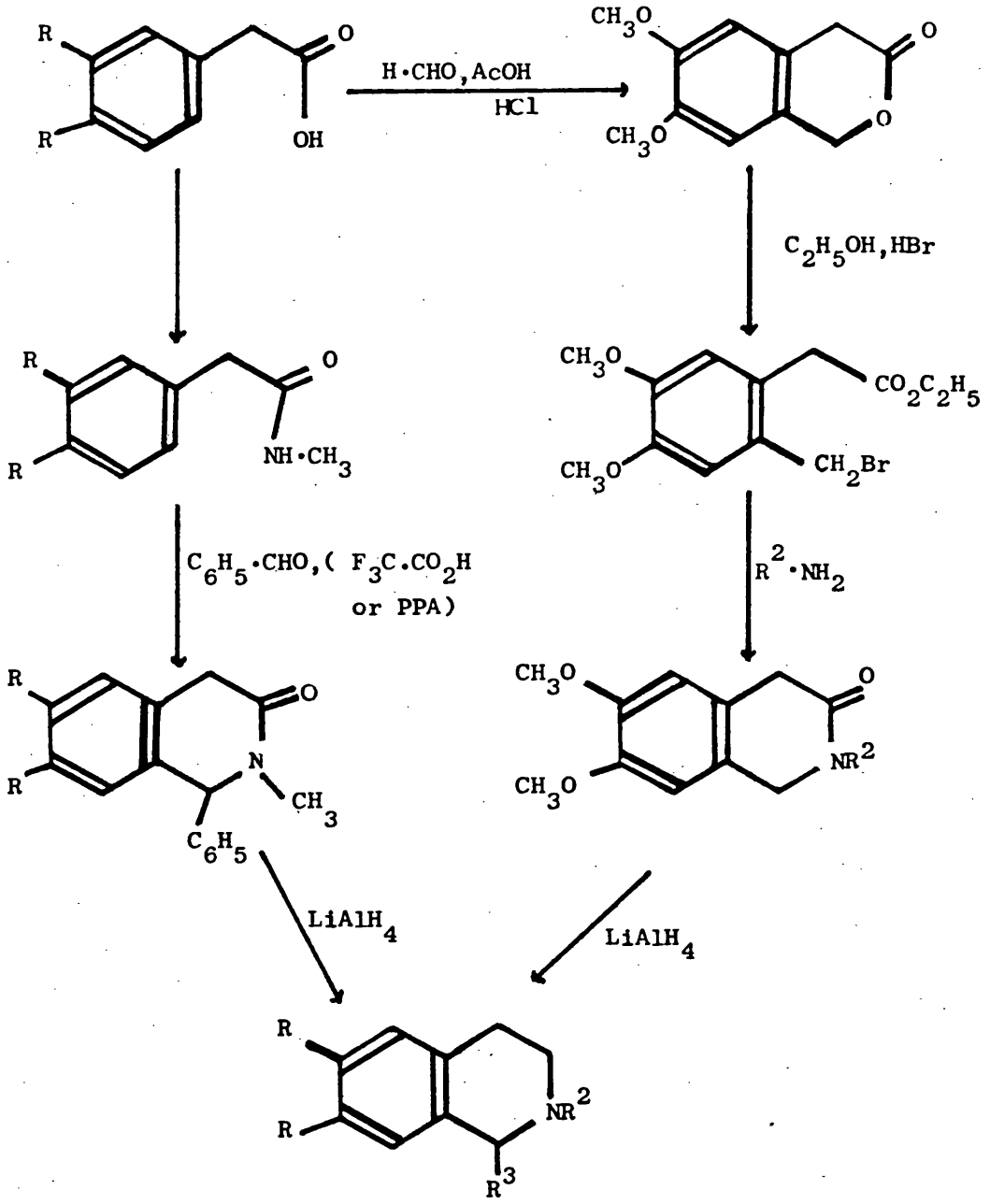
Ben Ishai et al.[319] have recently prepared isoquinolones(332), employing methanesulphonic acid(MSA) as reagent for cyclization.



(332)

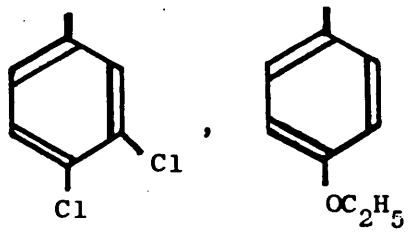
R=H, CH_3, CO_2CH_3

Scheme 35



R = H, OCH_3.

R^2 = CH_3,



R^3 = C_6H_5, H.

For the synthesis of Benzylisoquinolines, Bisbenzylisoquinolines, Cularines, Aporphines, Berberines, Benzophenanthridines, and other isoquinoline derivatives the reader is referred to the excellent review by Shamma.[320]

3.3

The biosynthesis and metabolism of isoquinoline derivatives is discussed in detail in the reviews by Shamma[320] and Mann.[321]

3.4

The isoquinoline derivatives, some of which occur naturally, possess a wide range of biological activity. A few of the many examples, are given in Table 7.

Table 7

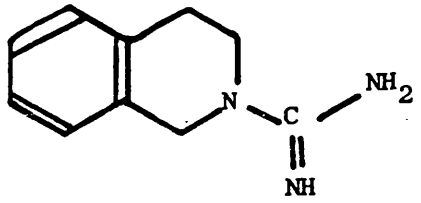
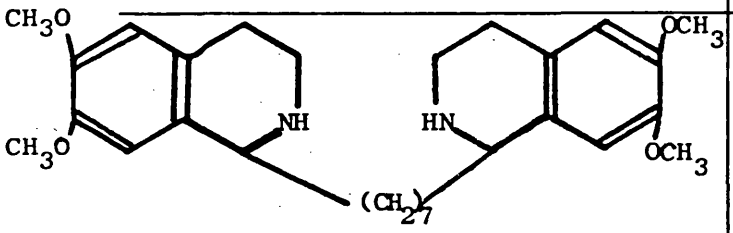
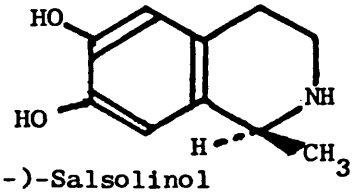
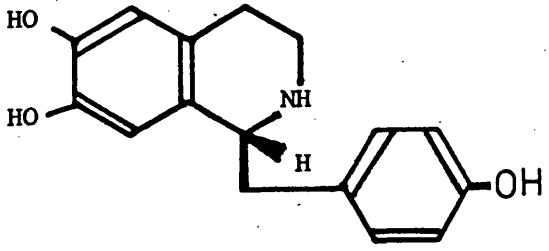
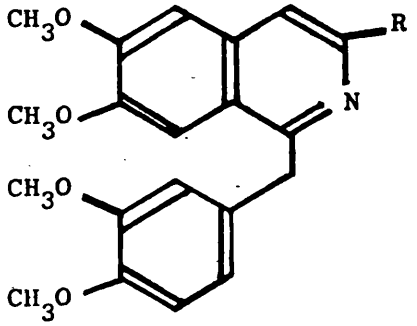
Isoquinoline Derivative	Pharmacological Activity	Reference
Debrisoquine 	Antihypertensive.	309
 Analogue of Bisobrin	Antithrombic.	322,323
 S-(-)-Salsolinol	Inhibitor of dopamine accumulation in brain.	324
	Smooth muscle and uterine relaxation.	325
 Papaverine (R = H) Dioxyline (R = CH_3)	Antispasmodic and peripheral vasodilator. Peripheral and coronary vasodilator.	326 327,328

Table 7 (Continued)

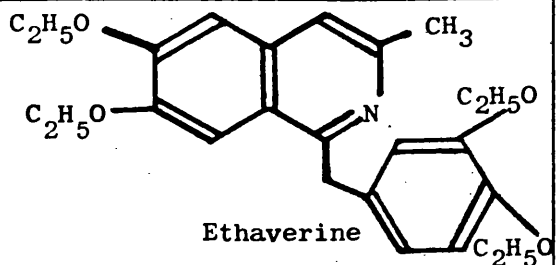
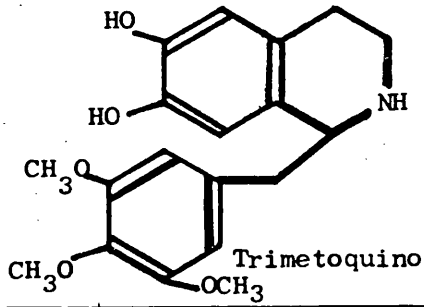
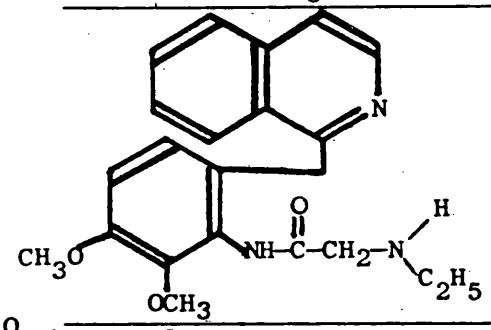
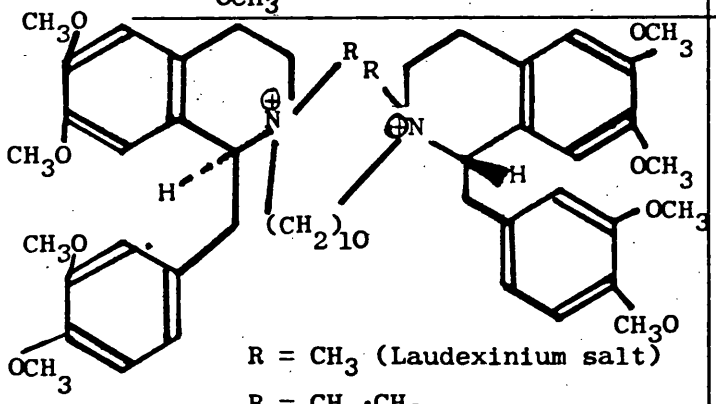
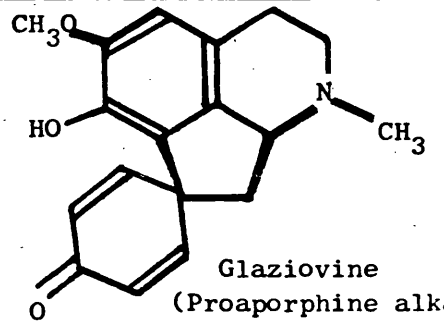
Isoquinoline Derivative	Pharmacological Activity	Reference
 Ethaverine	Smooth muscle relaxant.	326
 Trimetoquinol	Bronchodilatory and potent β-adrenergic.	326,329, 330
	Antiarrhythmic.	331
 R = CH_3 (Laudexinium salt) R = $CH_2 \cdot CH_3$ Quaternary dimers of tetrahydropapaverine (Bisbenzylisoquinolines)	Potent neuromuscular blocking agents.	332,333
 Glaziovine (Proaporphine alkaloid)	Tranquillizer. Analgesic and hypotensive.	334 335,336

Table 7 (Continued)

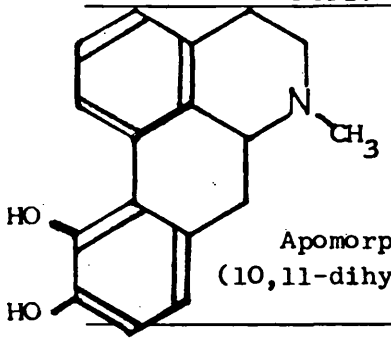
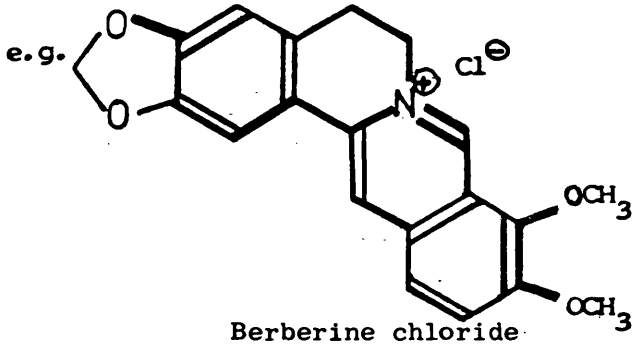
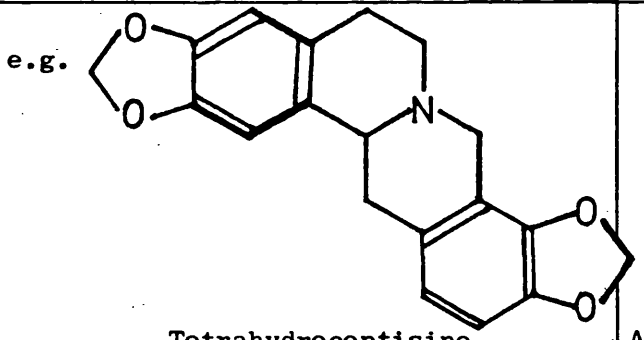
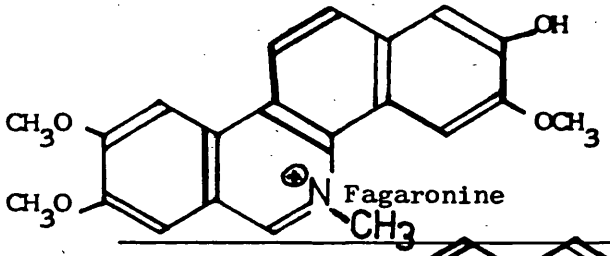
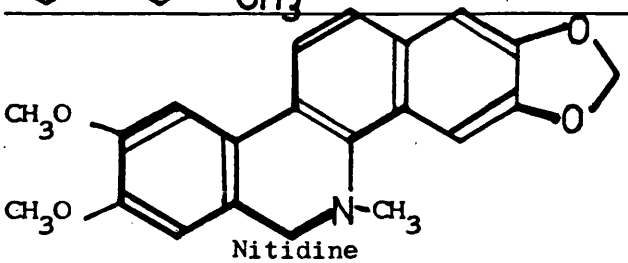
Isoquinoline Derivative	Pharmacological Activity	Reference
 Apomorphine (10,11-dihydroxyaporphine)	Stimulates the dopaminergic system. Anti-Parkinson. Hypotensive.	337,338 339
Protoberberine alkaloids, e.g.  Berberine chloride	Antimicrobial, uterine, and anti-leukemic/anti-neoplastic.	340,341, 342,343, 344
	Antifungal and antiarrythmic.	345,346, 347
e.g.  Tetrahydrocoptisine	Antipsychotic and neuroleptic.	348
 Fagaronine	Active in the P388 lymphocytic test.	349,350, 352
 Nitidine	Active in the P388 lymphocytic test and is strongly cytotoxic.	351,352, 353,354, 355,356.

Table 7 (Continued)

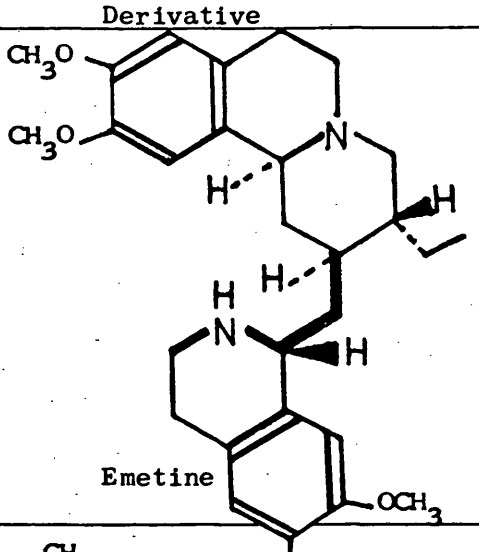
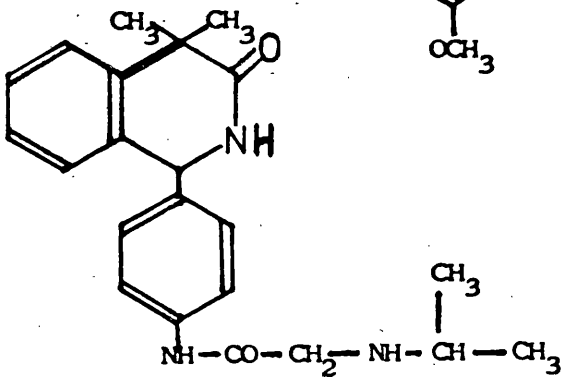
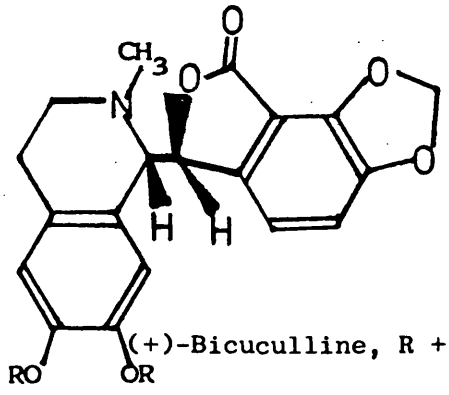
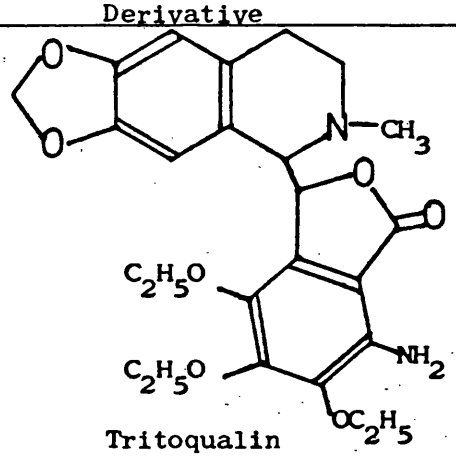
Isoquinoline Derivative	Pharmacological Activity	Reference
 Emetine	Inhibits protein synthesis by preventing the translation of amino-acyl transfer RNA to ribosomal peptide. It also inhibits *in vitro* aerobic glycolysis in cardiac muscle.	357,358, 359,360
 1-Phenylisoquinoline lactam	Anticonvulsant.	361
 (+)-Bicuculline, R + R = CH_2	Antagonises both the depressant effects of microiontophoretically applied GABA, and certain strychnine-resistant central inhibitions.	37b
(+)-Bicuculline methochloride	GABA antagonist.	77,78,362
(+)-Corlumine, R = CH_3	GABA antagonist	77,78

Table 7 (Continued)

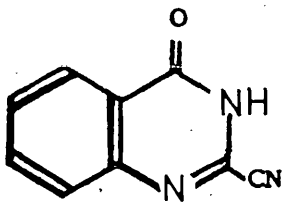
Isoquinoline Derivative	Pharmacological Activity	Reference
 Tritoqualin	Inhibitor of histidine decarboxylase.	363

CHAPTER FOUR

REVIEW OF QUINAZOLINES

4.1 Introduction

Although quinazoline itself was first synthesised by Bischler and Lang[365] in 1895 and Gabriel[366] in 1903, preparation of a quinazoline derivative(333) was reported by Griess[367] in 1869.



(333)

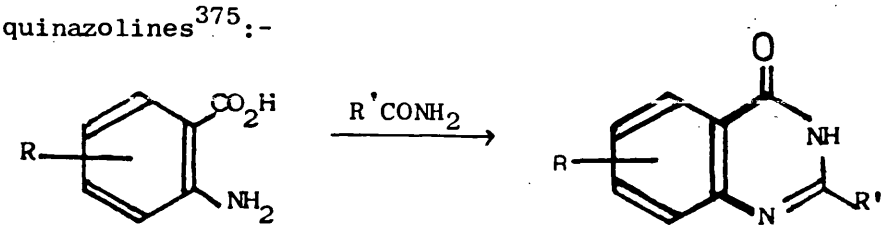
For an account of the history and early work in the field of quinazolines, the reader is referred to the reviews by Williamson[368] and Landquist.[369] The chemistry of quinazolines is discussed in depth by Armarego[370,371] and others.[411,418]

4.2 Synthesis of quinazolines

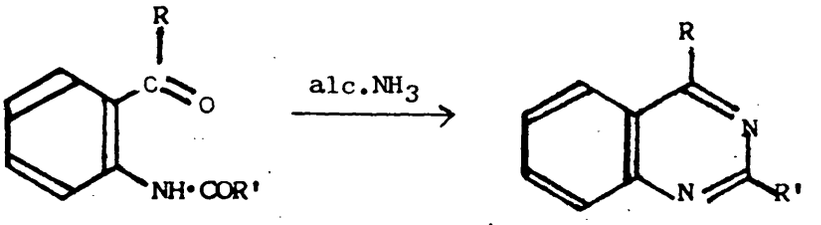
Quinazolines can be prepared either *via* a primary route or a secondary route.

a) The primary route leading to formation of quinazolines involves the building up of the quinazoline system from the intact carbocyclic ring, for example:-

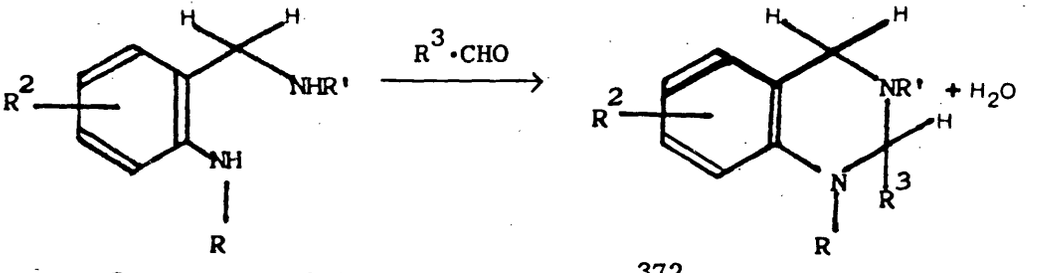
(i) Niementowski synthesis[374] (reaction of 'O'-aminobenzoic acids with amides) which yields 3,4-dihydro-4-oxo-quinazolines[375]:-



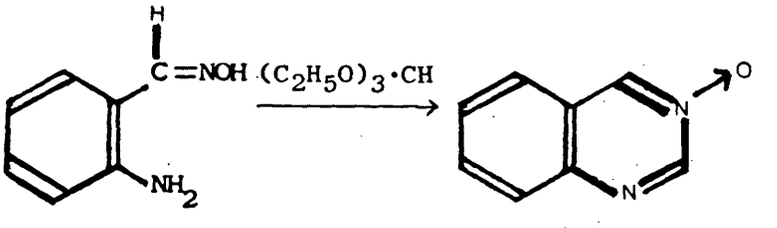
(ii) Bischler synthesis (reaction of 'O'-amidobenzaldehydes with ammonia)[376-378]:-



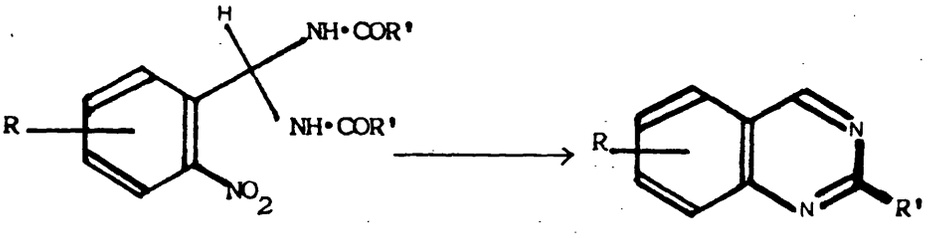
(iii) Reaction of 'O'-aminobenzylamines with aldehydes to yield 1,2,3,4-tetrahydroquinazolines[379,380]:-



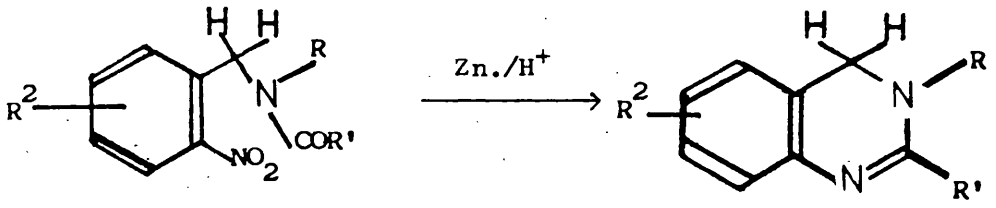
Reaction of 'O'-aminobenzaldehyde[372] or 'O'-aminophenyl ketone[373] oximes with ethyl orthoformate to yield quinazoline-3-oxides:-



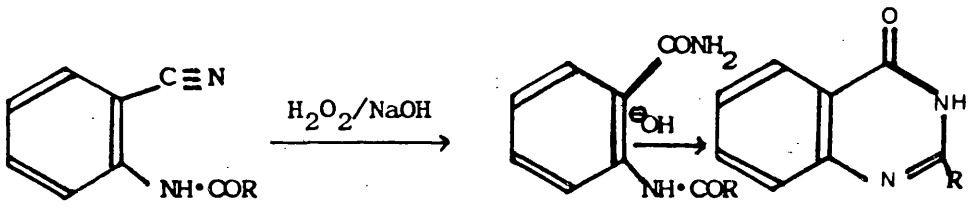
(iv) Riedel synthesis (reductive cyclization of bisamido-'O'-nitrobenzaldehydes[381-383]:-



Reductive cyclization of 'O'-amidomethylnitrobenzenes[366,379]:-

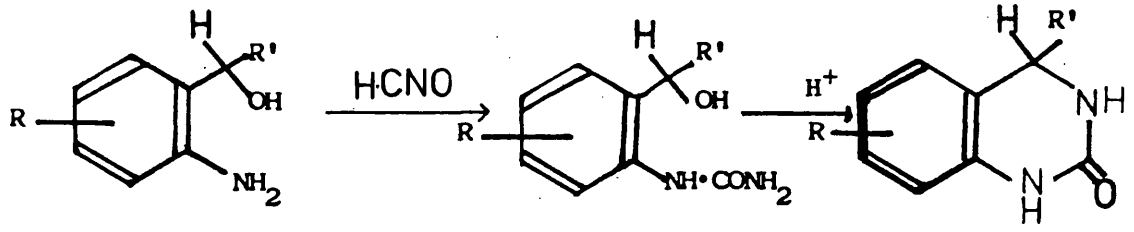


(v) Cyclization of 'O'-amidobenzonitriles with alkaline hydrogen peroxide[384-389] to yield 3,4-dihydro-4-oxoquinazolines:-

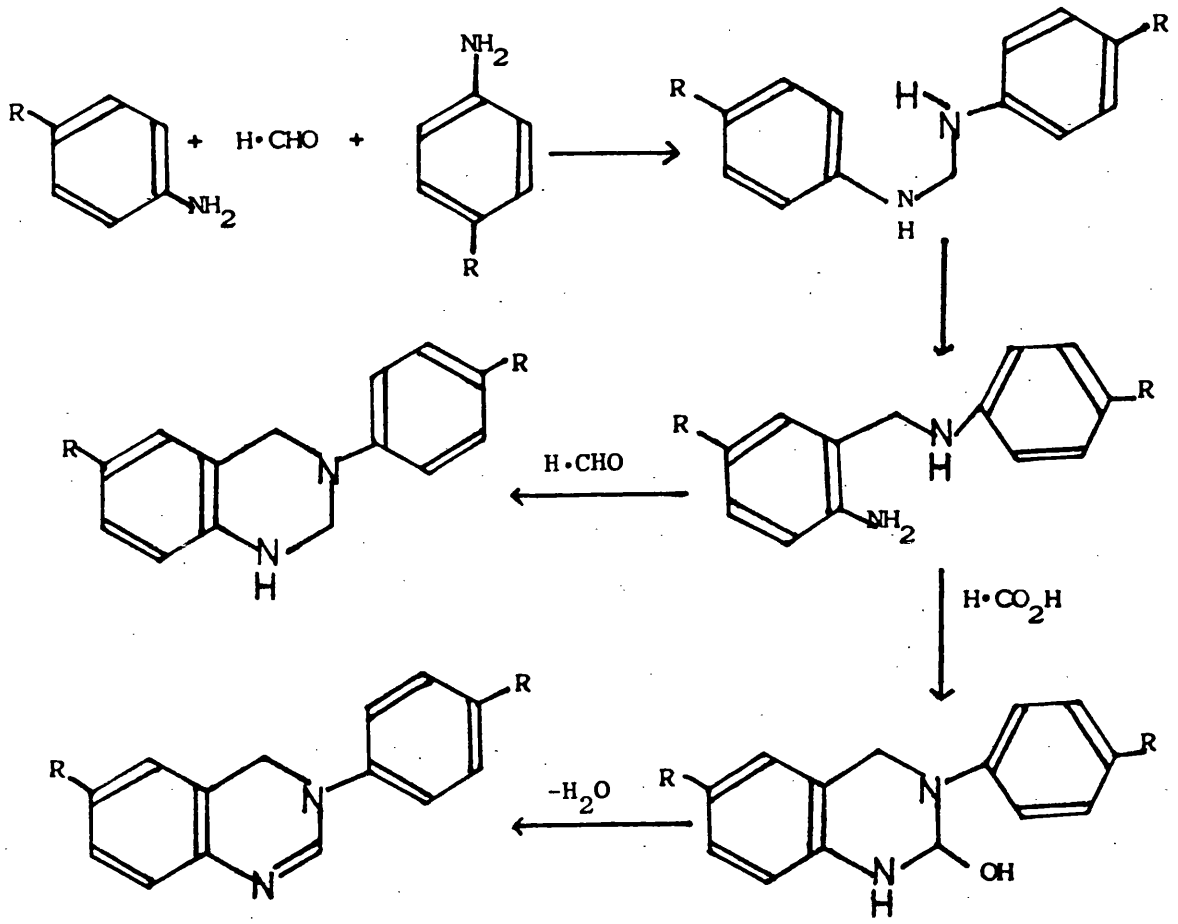


Cyclization of 'O'-amidoacetophenoneoximes with mineral acids to yield quinazoline-3-oxides.

(vi) Synthesis of 1,2,3,4-tetrahydro-2-oxoquinazolines from 'O'-ureidobenzyl alcohols[390-392]:-

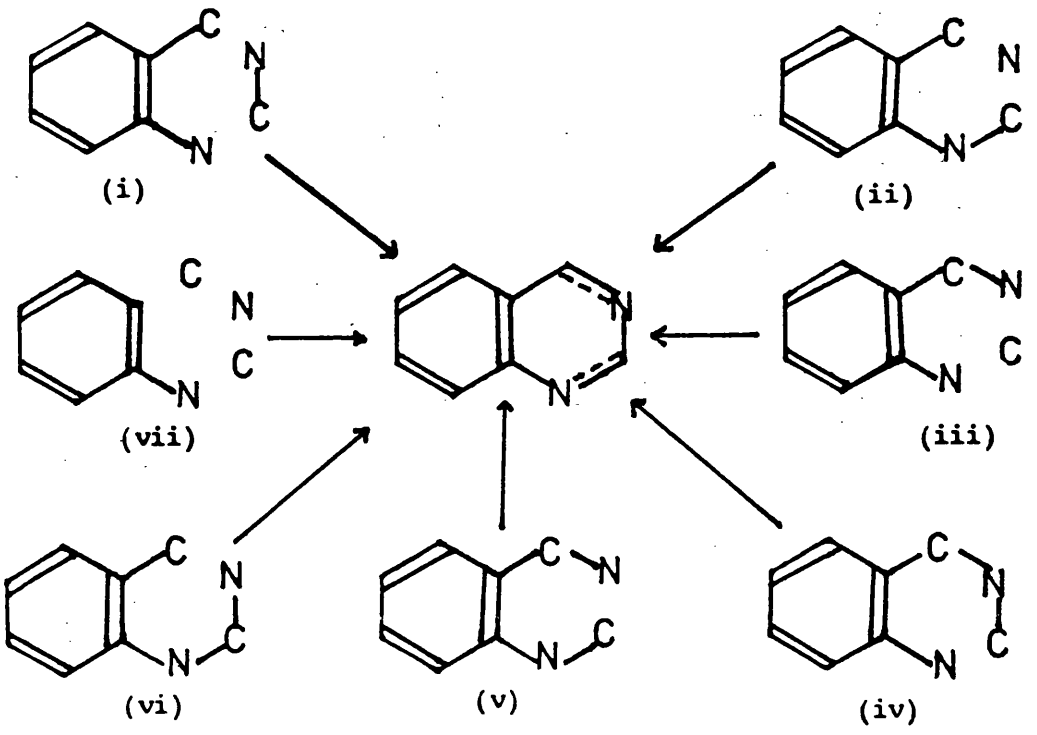


(vii) Synthesis of 3,4-dihydroquinazolines by reacting anilines with formaldehyde[393-399]:-

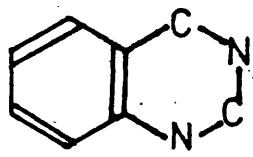


For a summary of the above seven primary syntheses, see Figure 10.

Figure 10



b) The secondary route leading to quinazoline formation, involves transformations on the intact skeleton(334),[406] the most important of which are oxidation, reduction,



(334)

the metathesis, addition, and substitution reactions (also involving side-chain reactions).

4.2.1

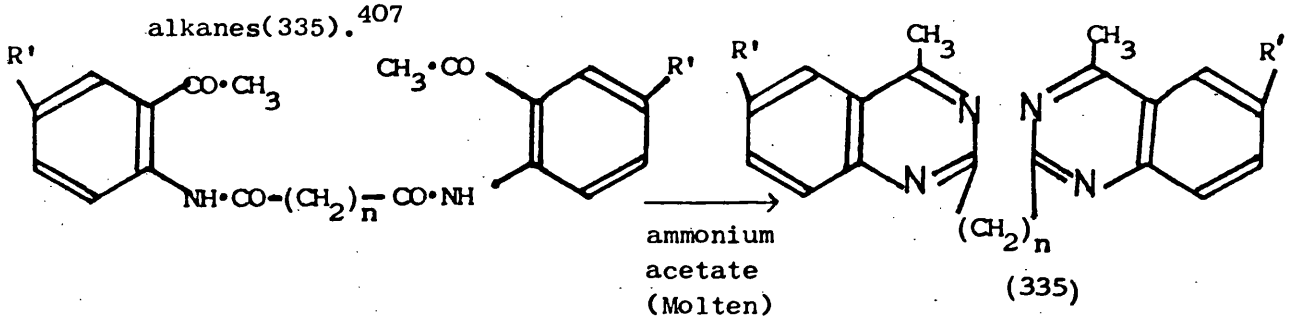
The following section attempts to review modifications of older synthetic methods and novel synthetic routes leading to the formation of quinazolines and their derivatives, up to the present date. During the past decade, interest in quinazoline synthesis has increased owing to the potent biological activity possessed by the various derivatives.

4.2.1.1

Gotthelf[400] reported the preparation and chemistry of several 2-alkyl-4-oxodihydroquinazolines from anthranilic acid, in 1901.

2,3-Disubstituted-4-quinazolones,[401] methyl quinazolines,[402] and quinazoline carboxylic acids[403] have been prepared by Bogert et al. Several 3-aryl-4-quinazolones were synthesised by Morgan et al.[404] 6,8-Disubstituted quinazolines[405] were (successfully) prepared in 1947.

The preparation of 4-phenylquinazolines[422,423] was reported by Schofield.[408] Schofield *et al.* also prepared some di-2-quinazolinyl-alkanes(335).[407]

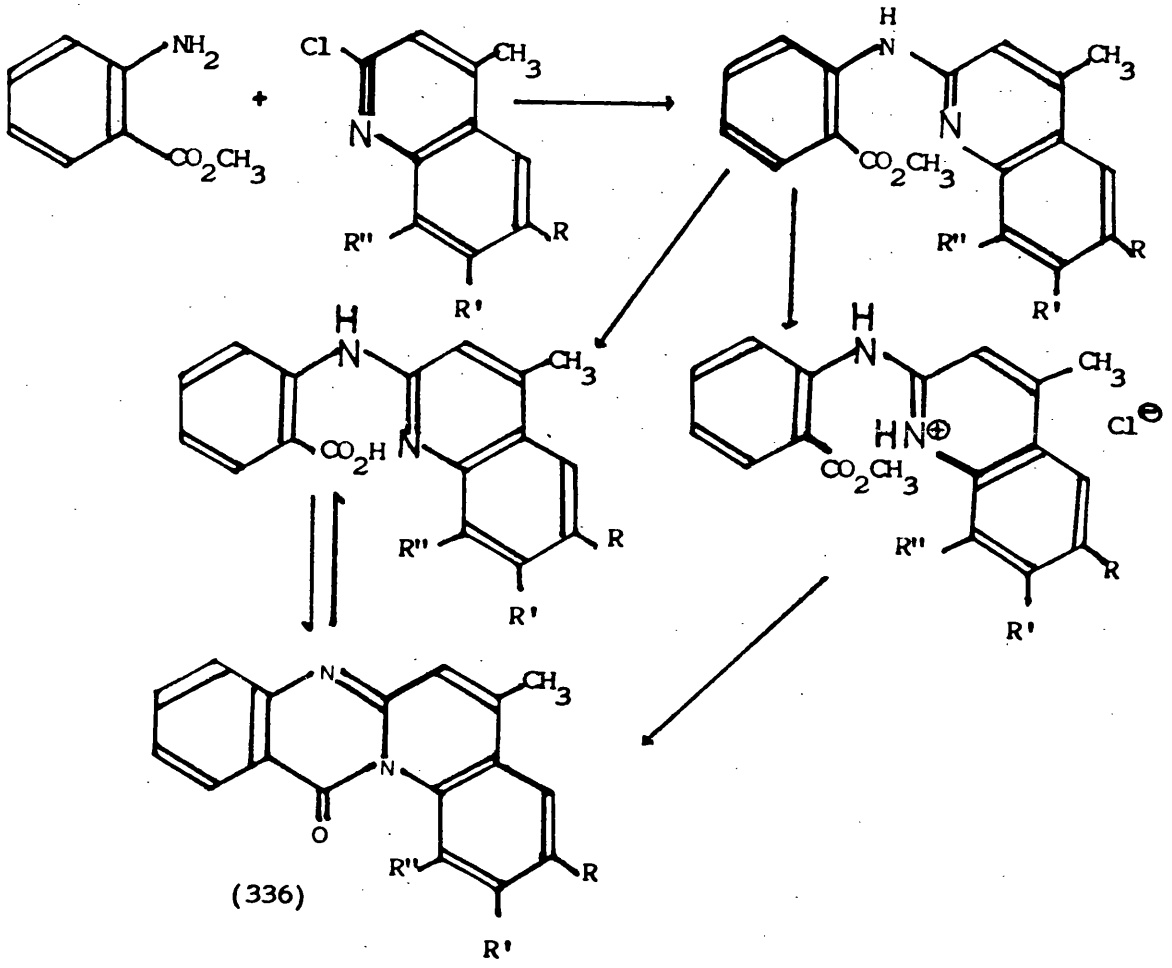


(335)

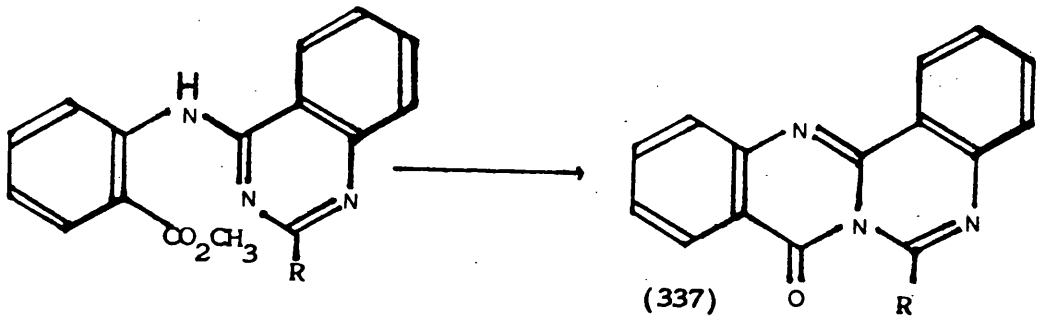
Condensation of anthranilates with cyclic imidoyl chlorides[409] affords quinazolines(336) and (337),[410] (see Scheme 36). 2-Aryl-4-quinazolones have been prepared by Stephen *et al.*,[412] and Eaton *et al.*[421]

The preparation of several 4-substituted quinazolines(338) has been reported by Chapman and Taylor.[413]

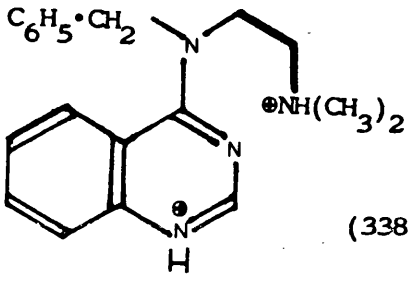
Scheme 36



(336)



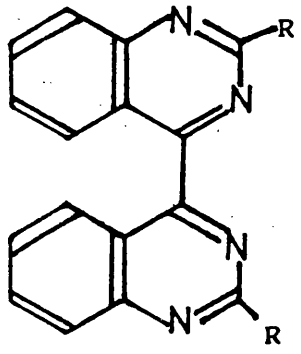
(337)



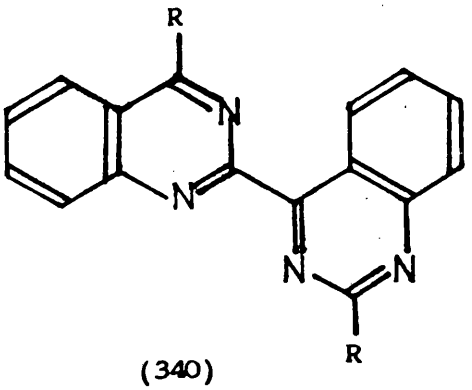
(338)

4.2.1.2

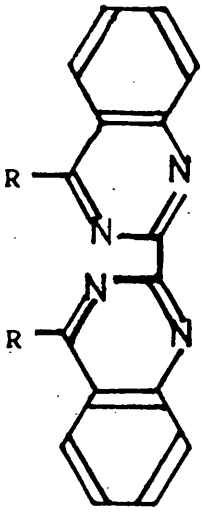
Quinazoline and 2- and 4-methylquinazolines react with aqueous sodium cyanide to give the dimeric biquinazolinyles[415] (339), (340) and (341).



(339)



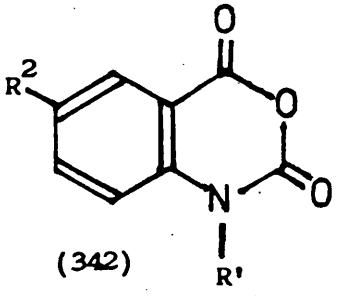
(340)



(341)

4.2.1.3

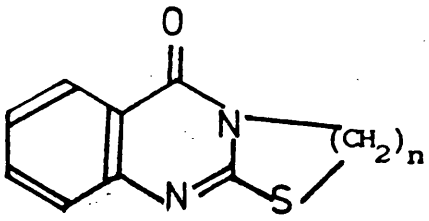
Several quinazoline derivatives have been prepared from isatoic anhydrides(342),[429,416,427,432] and their derivatives.[442]



(342)

4.2.1.4

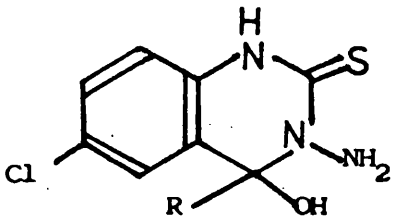
The thiazolo and thiazino analogues of febrifugine, 2,3-dihydro-5 H-thiazolo[2,3-b]quinazolin-5-one(343) and 3,4-dihydro-2H,6H[1,3]-thiazino[2,3-b]quinazolin-6-one(344), have been prepared by Payne et al.,[419] by the reaction of chloroalkyl isothiocyanates ($Cl[CH_2]_n \cdot N{=}C{=}S$) on methyl anthranilate.



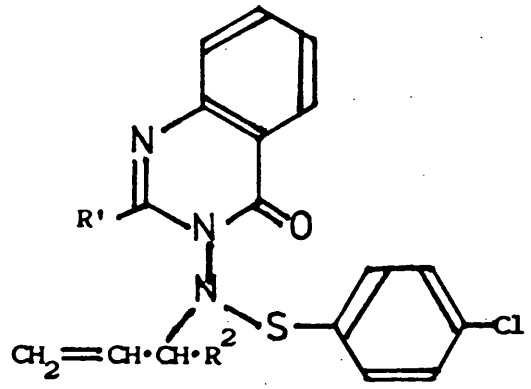
(343) n = 2

(344) n = 3

Several other sulphur-containing quinazoline derivatives have been prepared, including compounds (345)[420] and (346).[428]



(345)



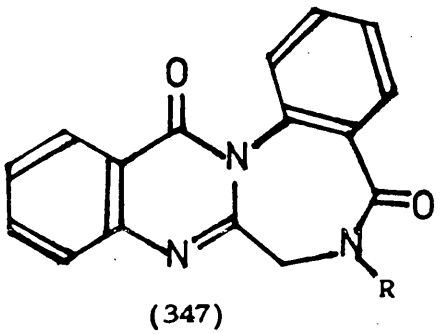
(346) (a) $R^1 = R^2 = CH_3$

(b) $R^1 = R^2 = H$

4.2.1.5

The formation of quinazolines from 1,4-benzodiazepines has been discussed by Sternbach[499] et al.,[414] Peet et al.,[435] and Bianchi et al.[426]

Taylor and co-workers[417] report the preparation of some quinazolino[3,2-a][1,4]benzodiazepines(347).



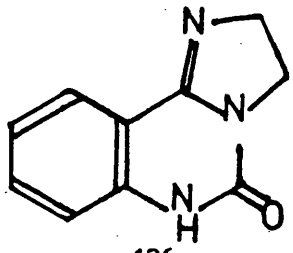
(347)

R = H, CH_3, C_2H_5, $CH_2 \cdot CH_2 \cdot OH$, NH_2, etc.

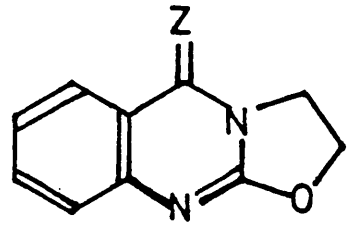
4.2.1.6

Recently, many quinazoline derivatives containing a fused third ring have been prepared (see Figure 11 for some examples). Derivatives (350, (351) and (352) are potential narcotic antagonists.

Figure 11

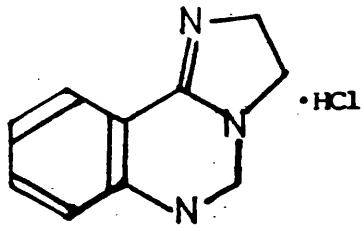


(348)[436]



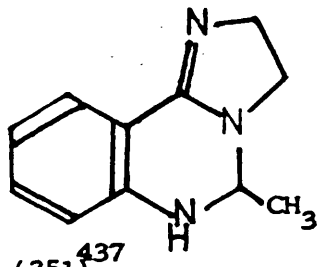
Z = NH, O

(349)[436]

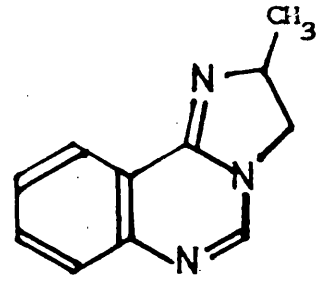


(350)[437]

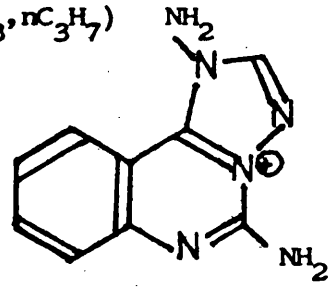
(R = H, CH_3, nC_3H_7)



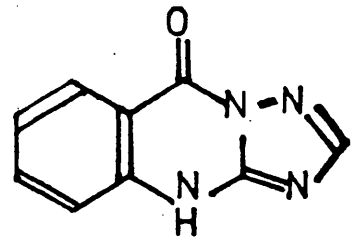
(351)[437]



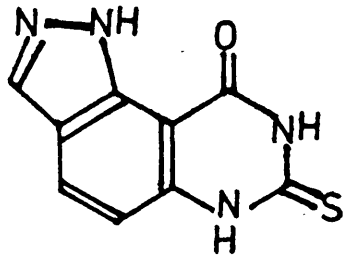
(352)[437]



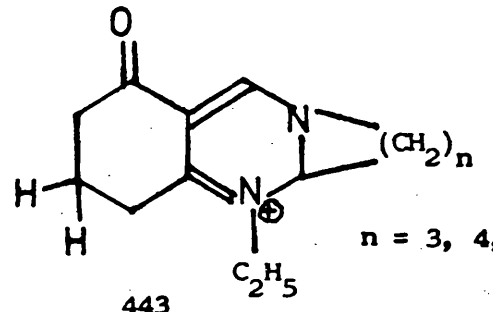
(353)[425]



(354)[425]



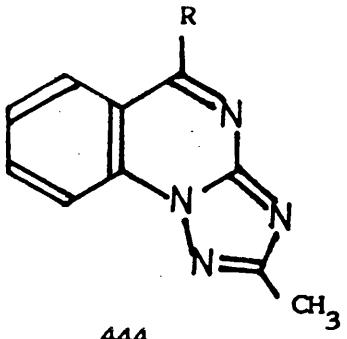
(355)[441]



n = 3, 4, 5.

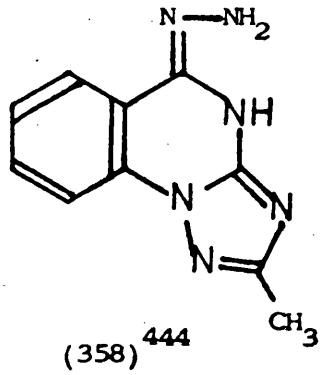
(356)[443]

Figure 11 (Continued)

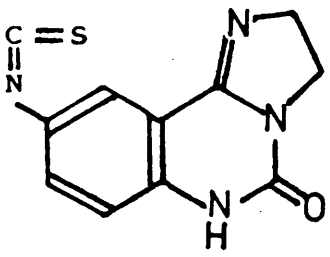


(357)[444]

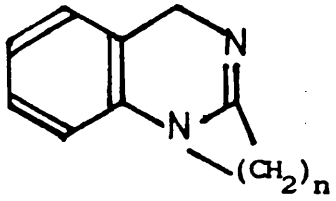
R = Cl, $N(CH_3)_2$, NH_2, etc.



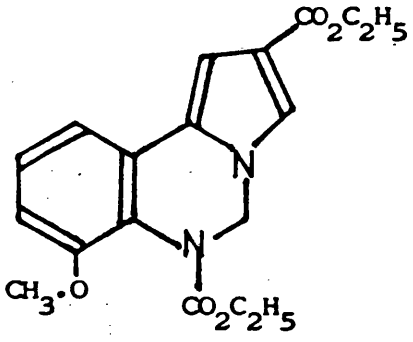
(358)[444]



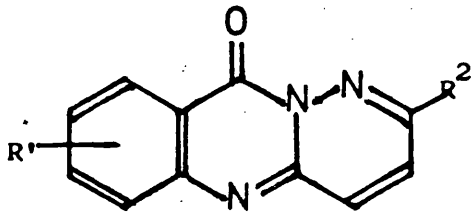
(359)[445]



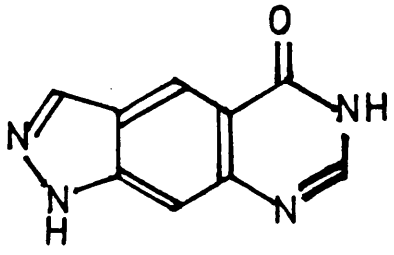
(360)[448] n = 3,4,5.



(361)[449]



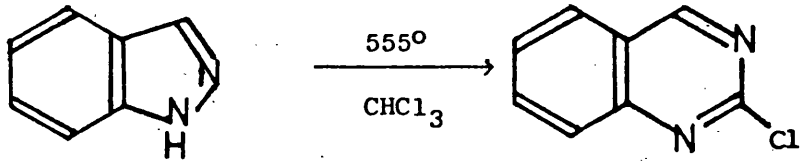
(362)[440]



(363)[447]

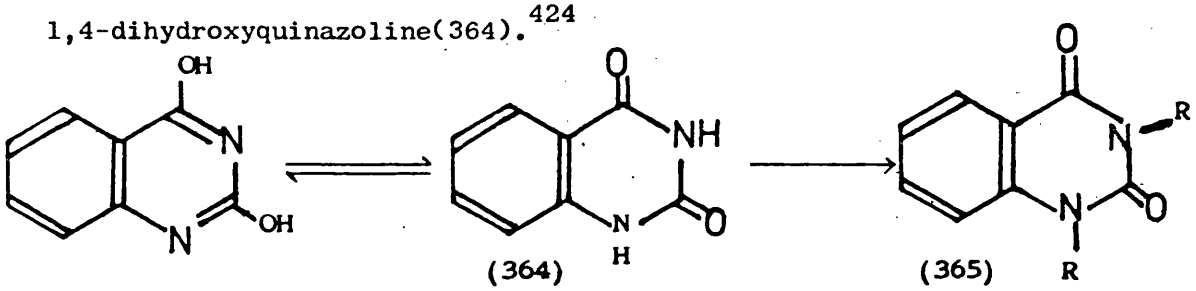
4.2.1.7

Busby *et al.*[430] report the synthesis of 2-chloroquinazoline(366) *via* pyrolysis of (367).



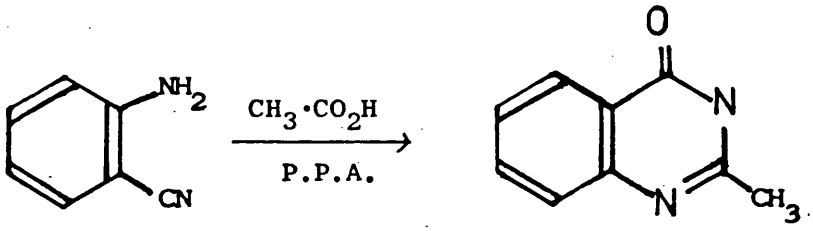
(367) (366)

A series of dialkylquinazolinediones(365) have been prepared from 1,4-dihydroxyquinazoline(364).[424]



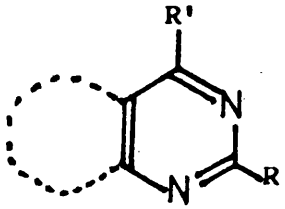
(364) (365)

Condensation of 'O'-aminobenzonitrile with acetic acid in the presence of polyphosphoric acid afforded 2-methyl-4-quinazolone(368).[431]



(368)

A general method for the preparation of condensed pyrimidines(369) from nitriles under acidic conditions is reported by Dave *et al.*[438]

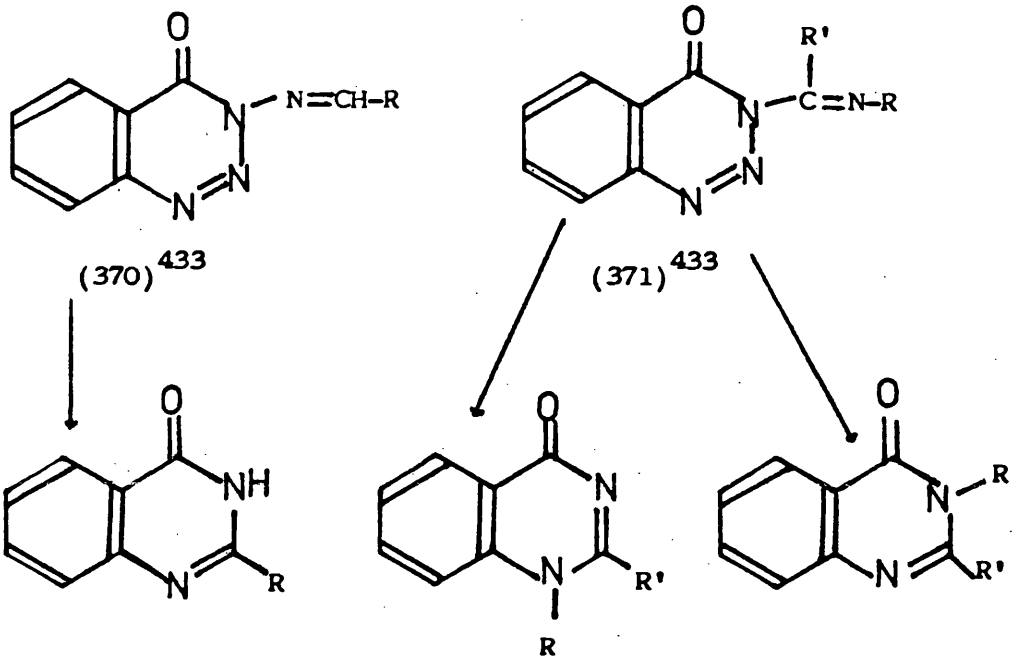


(369)

R^1 = NH_2, OH, etc.

R = H, Cl, etc.

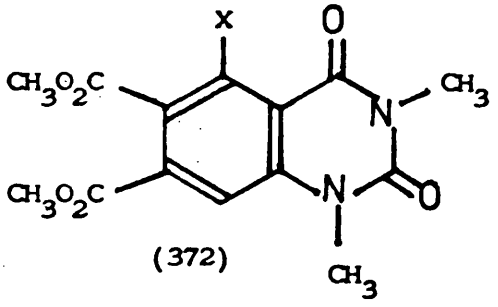
2-Arylquinazolin-4-ones and 1,2-diaryl-1,4-dihydroquinazolin-4-ones have been prepared by the thermal decomposition of 3-aryl-ideneamino-(370) and 3-imidoyl-(371) 1,2,3-benzotriazin-4-ones, respectively.[433]



(370)[433]

(371)[433]

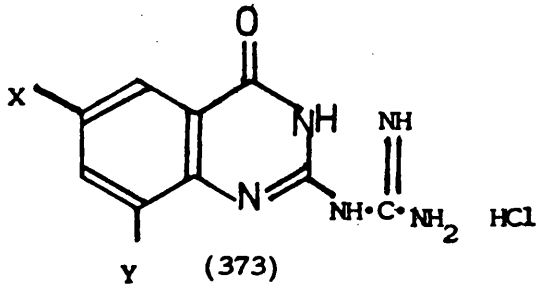
A novel synthesis of substituted quinazolines(372) is reported by Senda et al.[446]



(372)

X = H; CH_3; OH

6,8-Disubstituted 2-guanidino-4(3H)-quinazolinones[439] (373) have been prepared as potential antifungal agents.

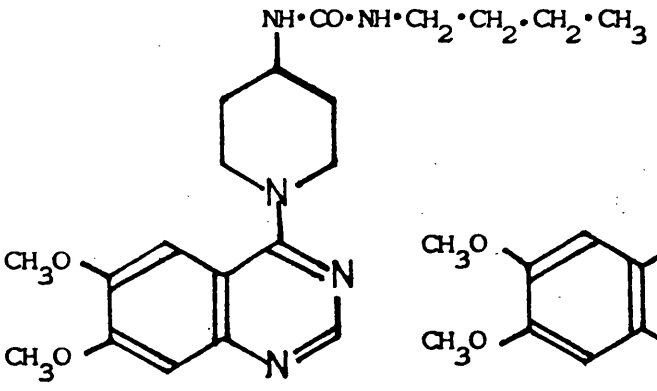


(373)

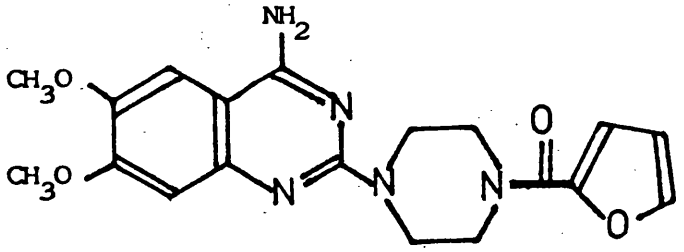
X = H; Br; I; Cl.

Y = H; Br; I; Cl.

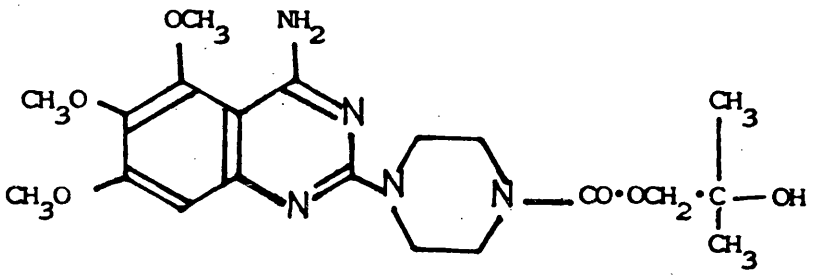
A group from Pfizer (U.K.) Ltd. discuss the substituted quinazolines (374), (375) and (376).[434]



(374)



(375)

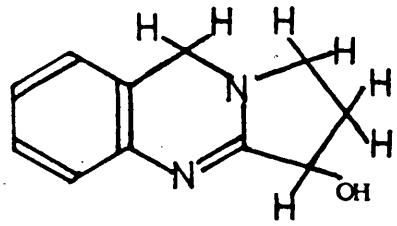


(376)

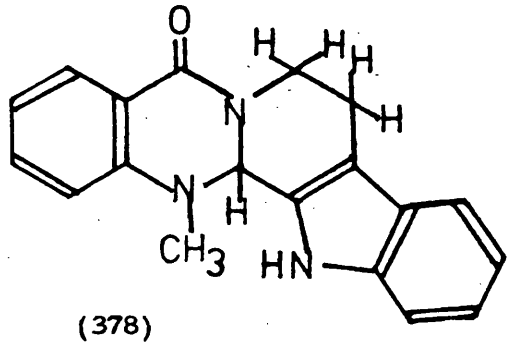
4.3 Biological activity in quinazolines and their derivatives

4.3.1

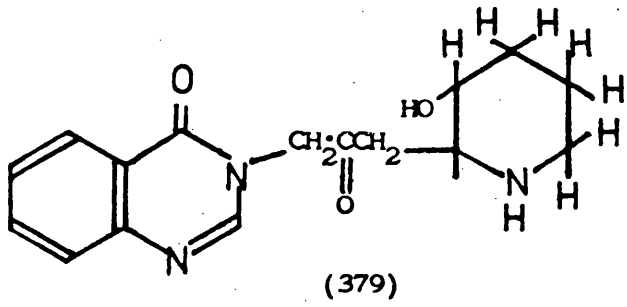
Few naturally occurring alkaloids possess the quinazoline nucleus and only some of these are pharmacologically active.[370] The vasicine(377) group[450,451] exhibits bronchodilator activity,[452,453] evodiamines(378)[354,355] show hypotensive activity, and the fabrifugines(379)[456,457] show high antimalarial activity.[458-462] The most active quinazoline known to date is the 2-iminoperhydroquinazoline,[466,467] tetrodotoxin(380),[463,464] which is a potent neurotoxin.[465]



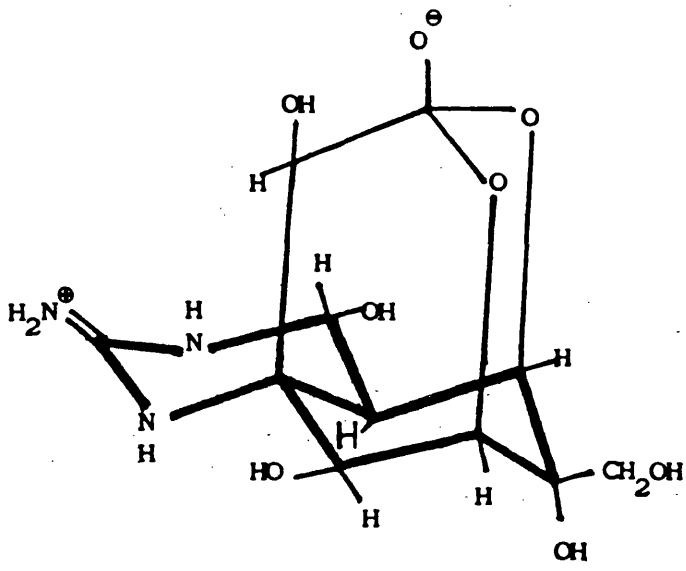
(377)



(378)



(379)



(380)

4.3.2

Many synthetic quinazolines have been tested for various biological activities, some of which are found to have specific activity. The hypnotic (methaqualone) and the oral diuretic (quinethazone), have been marketed and are used clinically with considerable success. The biological activities of some quinazolines[371] are listed in Table 8.

Table 8

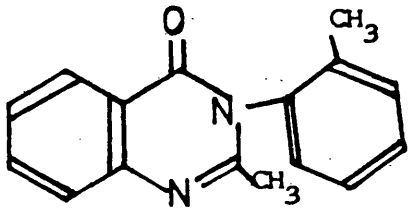
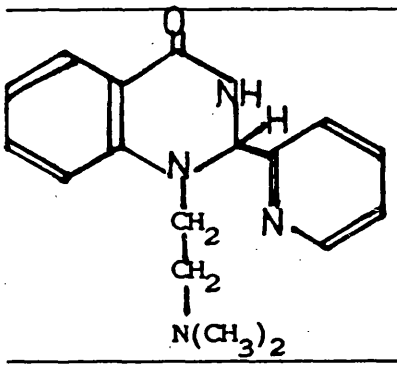
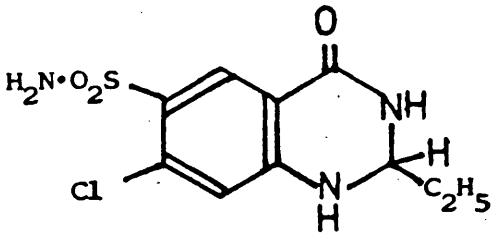
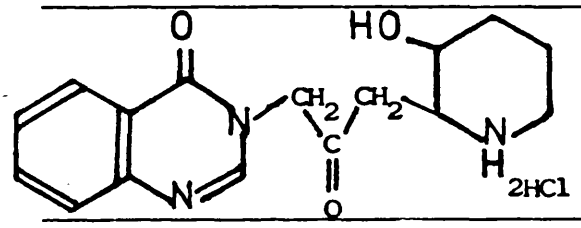
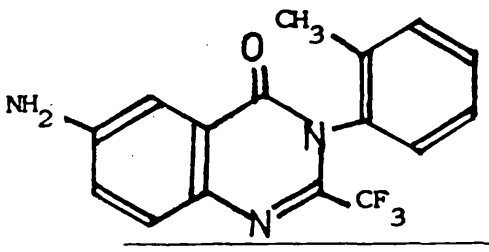
Quinazoline	Activity	Reference
 'Methaqualone'	Hypnotic and anti-convulsant.	468-472, 371,486, 491
	Antihistamine with low toxicity and minimal sedating side effects.	473
 'Quinethazone'	Oral diuretic.	474-476
Several amino-, guanidino-, and oxo-quinazolines	Antibacterial.	477-479
Some oxoquinazolines	Antiviral.	480-482, 496
	Antimalarial.	483
	CNS depressant.	484

Table 8 (Continued)

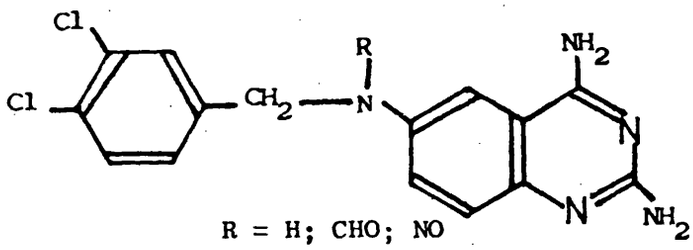
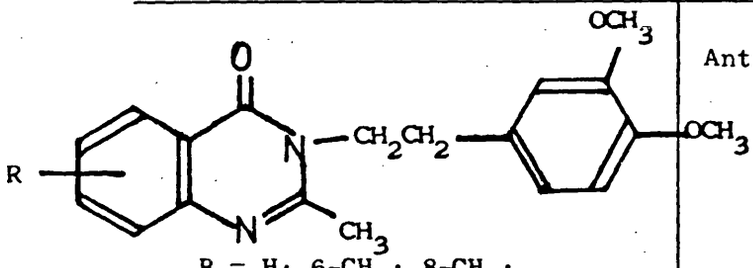
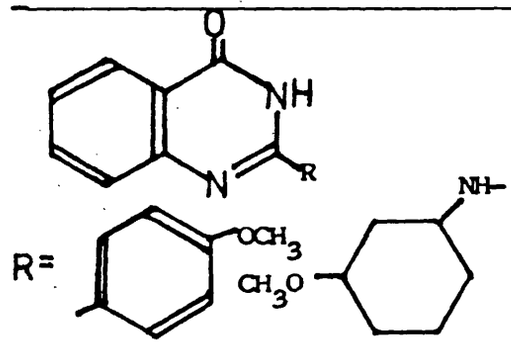
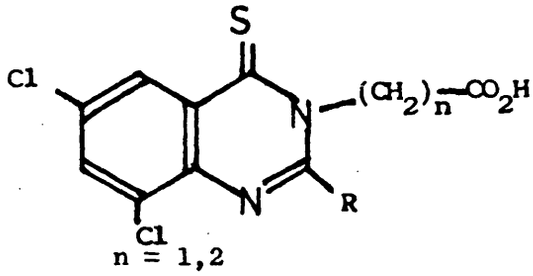
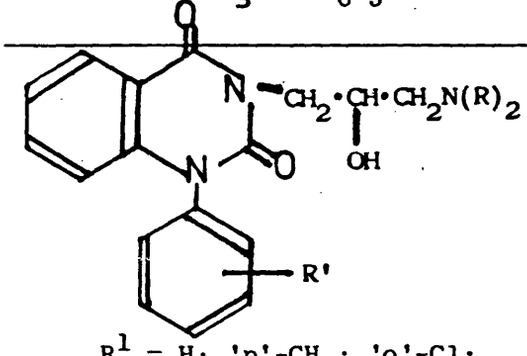
Quinazoline	Activity	Reference
 R = H; CHO; NO	Antimalarial.	485
 R = H; 6-CH_3; 8-CH_3; 6-Cl; 7-Cl; 6-I.	Antiparkinsonism.	487
	Antifertility.	488
 n = 1,2 R = H; CH_3 ; $-C_6H_5$	Anti-inflammatory.	489
 R^1 = H; 'p'-CH_3; 'o'-Cl; 'o'-CH_3	β-Adrenergic blocker.	490

Table 8 (Continued)

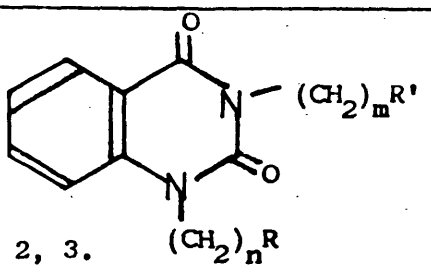
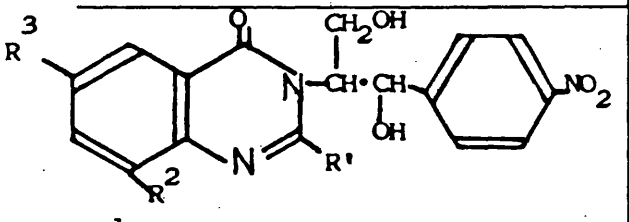
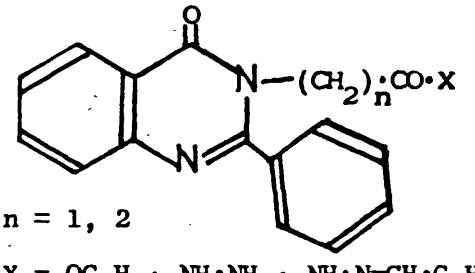
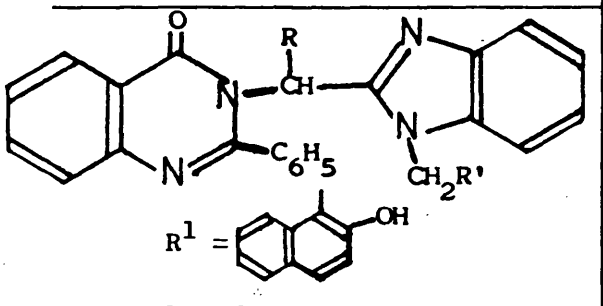
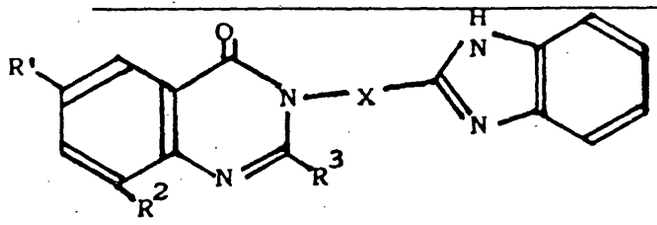
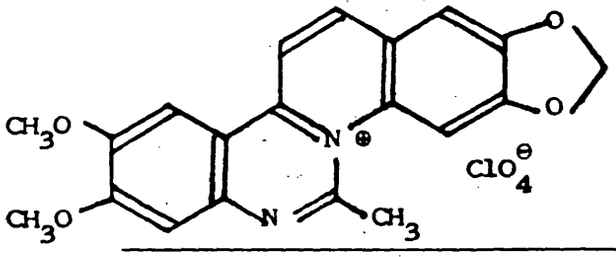
Quinazoline	Activity	Reference
R = butylamino; piperidino; morpholino; diethylamino; cyclohexylamino.		
 n = 0, 2, 3. m = 2, 3, 4, 5, 6, 7. R = H; $(CH_3)_2 \cdot N$; $(C_2H_5)_2 \cdot N$ R^1 = $C_6H_5 \cdot N(C_2H_5)_2 \cdot N$.	Peripheral vasodilator and antihypertensive.	492
 R^1 = $-CH_3$; $-C_6H_5$ R^2 = H; Br; Cl R^3 = H; Br; Cl; NO_2	Antibacterial.	493
 n = 1, 2 X = OC_2H_5; $NH \cdot NH_2$; $NH \cdot N{=}CH \cdot C_6H_4 \cdot R$ R = NH_2; NO_2; Cl; H; OCH_3	Antibacterial.	494
 R^1 = R = H; CH_3	Antiviral.	495

Table 8 (Continued)

Quinazoline	Activity	Reference
 R^1 = H; Br; I R^2 = H; Br R^3 = C_6H_5; CH_3 X = 'o'-C_6H_4; 'm'-C_6H_4; 'p'-C_6H_4	Anticonvulsant.	497
	Antitumour.	498

PART II. RESULTS AND DISCUSSION

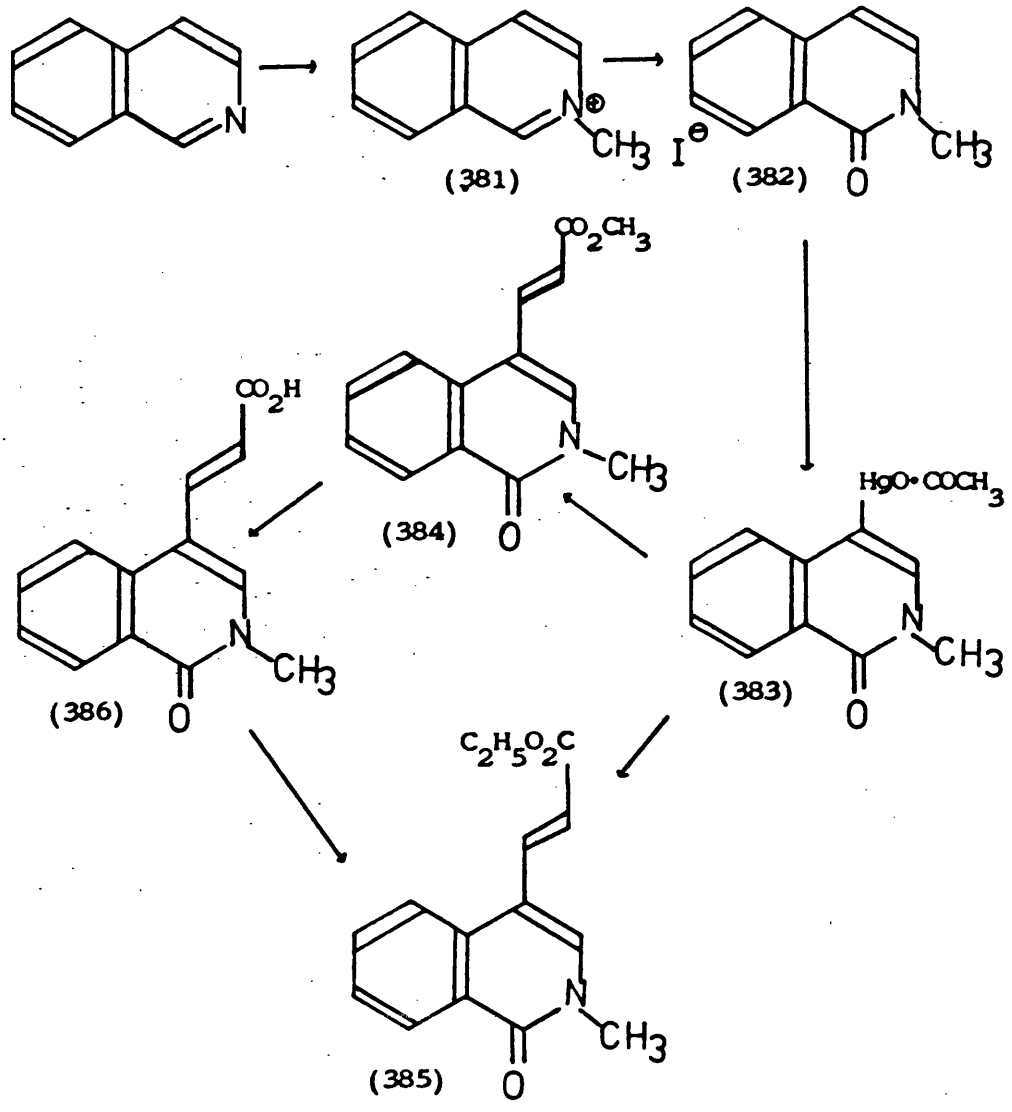
CHAPTER FIVE

SYNTHESIS OF AZASTEROIDS FROM ISOQUINOLINE DERIVATIVES

5.1 Preparation of dienes (384) and (385) from isoquinoline (See Scheme 37)

5.1.1 The methiodide (381) obtained in almost quantitative yield by reacting isoquinoline with methyl iodide, was oxidized with alkaline potassium ferricyanide to give the isoquinolone (382).

Scheme 37

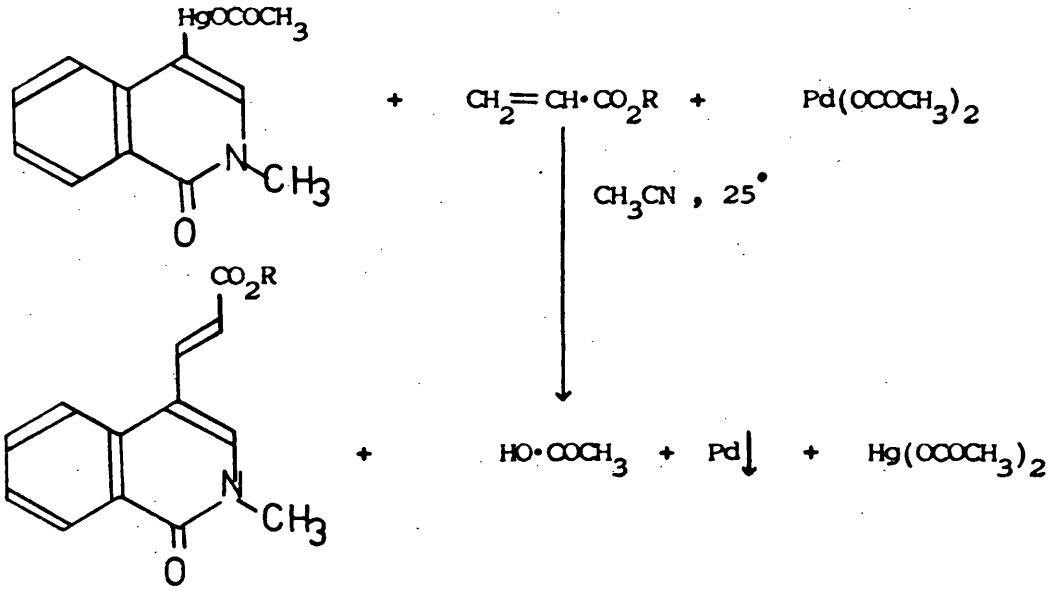


5.1.2 Mercuration (electrophilic substitution) of the isoquinolone (382) with mercuric acetate, occurred at the 4-position, as expected, to afford the acetate (383).

5.1.3 Organomercury compounds are known to undergo palladium-'catalysed' vinyl substitutions.[532] The palladium II salt may sometimes be used in 'catalytic' amounts provided an oxidant such as copper II chloride or mercury II acetate is present in order to regenerate the palladium II cation after each reaction cycle[533] for further reaction. In the absence of a suitable oxidant, stoichiometric amounts of the organomercury compound and palladium II salt must be employed.[534]

Reaction of the organomercuric acetate (383) (1 equivalent) with methyl acrylate (in excess) in the presence of palladium II acetate (1 equivalent), dissolved in a polar solvent such as acetonitrile, yielded the diene (384). Repetition of the above with the ethyl ester of acrylic acid in place of the methyl ester, furnished the diene (385). The yields were optimised by varying the concentrations of the reactants employed and the reaction time. Reactions were followed by thin layer chromatography until complete loss of starting material (383) was observed. Finally, the black precipitated palladium was separated from the product by filtration through a 'Celite' bed (ca. 3 cm. depth) on a sintered funnel. Some product which had adsorbed onto the filter aid was extracted with chloroform. After removal of solvents, from the combined extracts and filtrates, under reduced pressure, the product was purified by crystallization from acetonitrile assisted with decolourizing charcoal.

Overall reaction:-

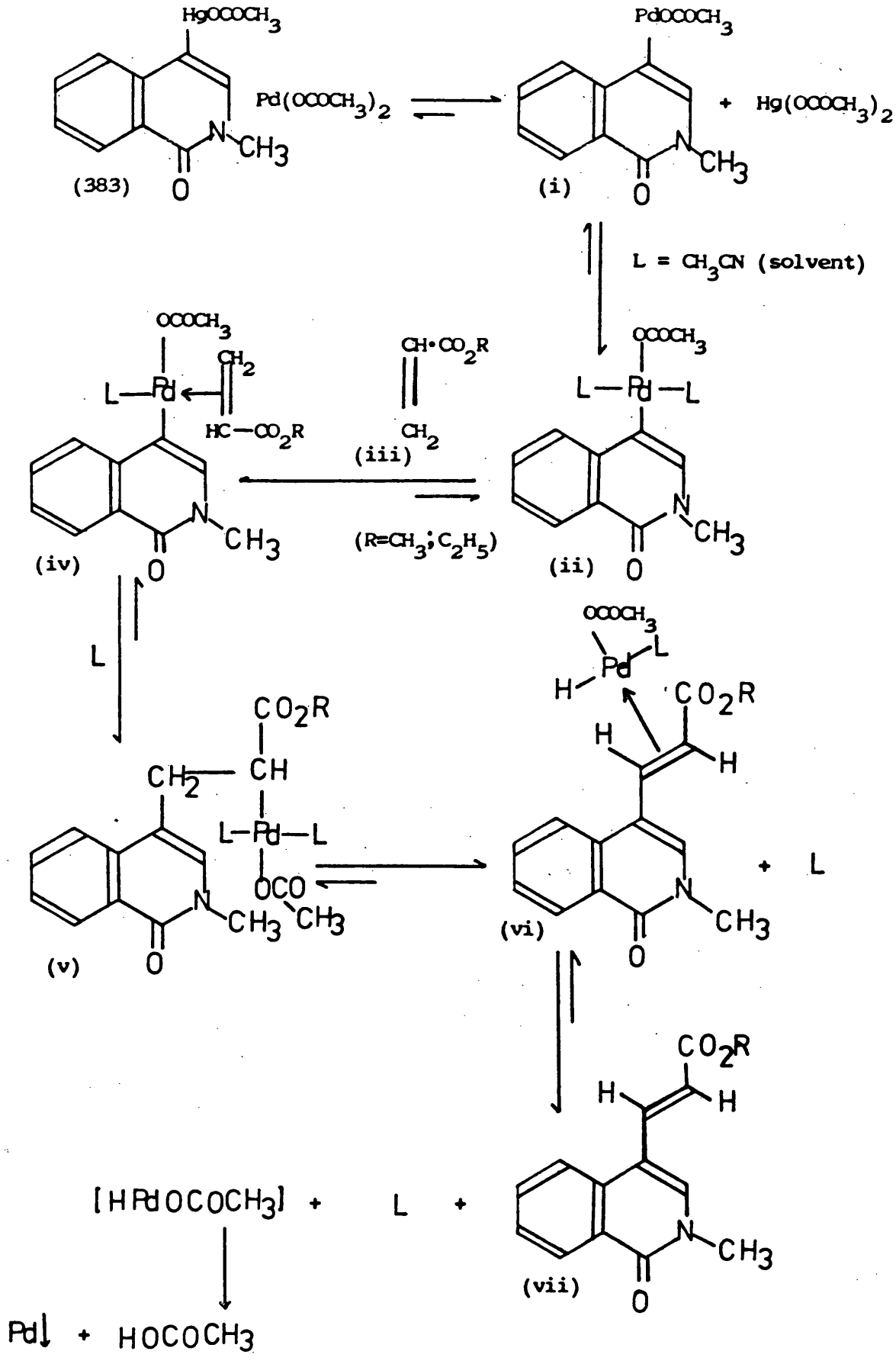


R = CH_3, C_2H_5

*Note 25° is used to denote average laboratory temperature.

From the above equation it can be noted that the mercury II acetate generated by the reaction may oxidize the palladium $\underline{0}$, formed at the end of a reaction cycle, to palladium II and so enable it to react further. When experiments were repeated employing catalytic amounts of palladium II acetate (ca. 0.1 equivalent), the total time taken for all the starting material (383) to react was greatly increased (>6 days), thus making this modification unfeasible. However, on an industrial scale, where expense of starting materials is important, this may be an important factor to consider against the time involved.

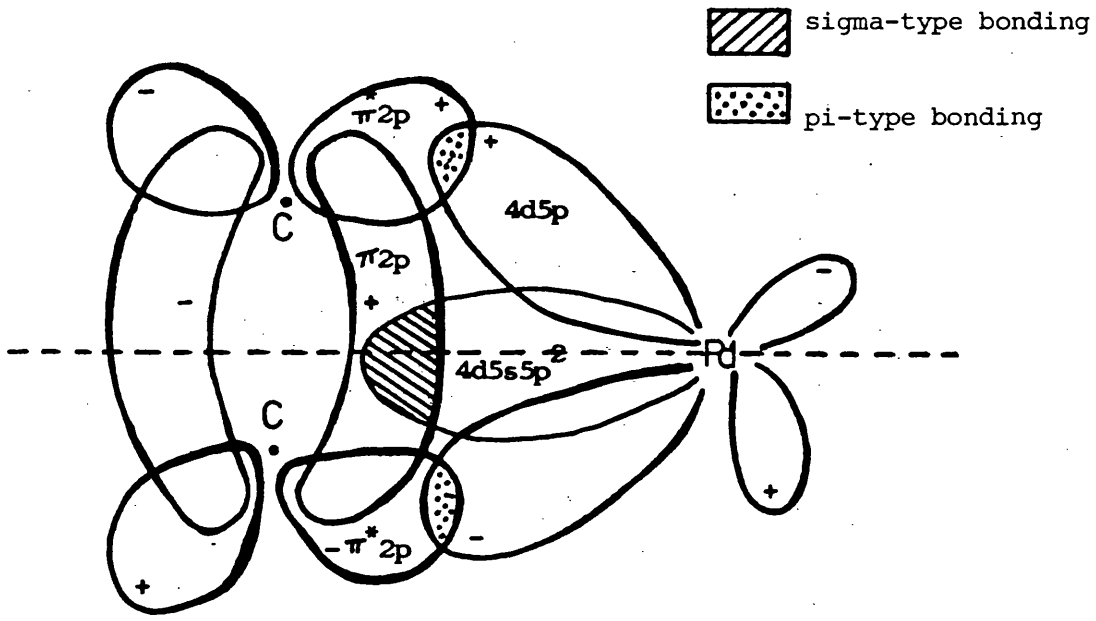
Scheme 38


HgOCOCH3
Pd(OCOCH3)2
(383)
PdOCOCH3
+ Hg(OCOCH3)2
(i)
L = CH3CN (solvent)
OCOCH3
L—Pd—L
(ii)
CH·CO2R
CH2
(iii)
(R=CH3;C2H5)
CH2
Pd
HC—CO2R
(iv)
L
CO2R
CH2—CH
L—Pd—L
OCO
CH3
(v)
H
Pd
(vi)
+ L
[HPdOCOCH3] + L +
Pd↓ + HOCOCH3
(vii)

The mechanism of this reaction is outlined in Scheme 38. The solvated arylpalladium salt (ii) (See Scheme 38) formed in situ by the exchange reaction of palladium acetate with the arylmercuric salt (383),[535] reacts readily with an olefin (iii) resulting in the formation of pi-bonded olefin complex (iv). The square planar intermediate (iv) with a co-ordination number of 4, undergoes rearrangement giving rise to the more stable sigma-bonded complex (v). Spontaneous elimination of ligands (solvent molecules) and hydridopalladium acetate[533] results in the formation of the stable trans product (vii).

The nature of the metal-olefin bond can be explained in terms of the molecular orbital theory.[536] Essentially,

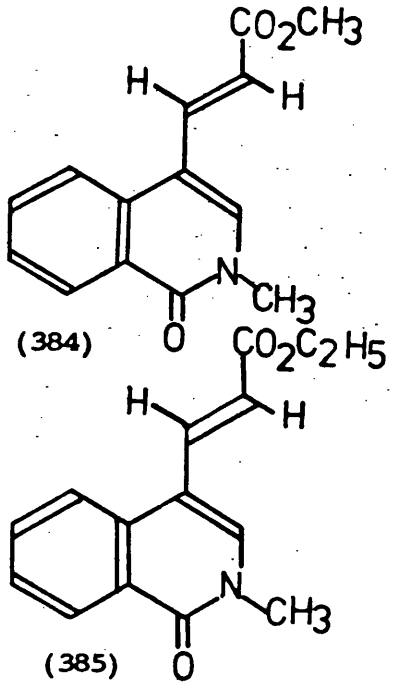
Figure 13



this involves a sigma-bond (olefin to metal) and a pi-bond (metal to olefin) as shown in Figure 13. The sigma-bond formed between the filled olefin pi orbitals and the empty $4d5s5p^2$ hybrid orbital on palladium results in unfavourable

distribution of negative charge on the metal ion. However, this situation is relieved by pi back-donation from the filled 4d5p hybrid orbital on palladium to the empty olefin antibonding pi (π^*) orbital, thus behaving in a synergistic manner. A prerequisite to this type of bonding is that the carbon-carbon double bond of the olefin lies perpendicular to the plane containing the metal and other ligand (L) atoms [Pd. L_3. (Olefin)] . The nature of the olefinic double bond (affected by substituents on one or both carbon atoms) and the solvating ligands (orbitals of which may be involved in the formation of hybridized orbitals), plays a vital role in the above mechanism.

Proton magnetic resonance spectroscopy may be used to assign the stereo-chemistry of a compound, provided the spectrum obtained is not too complex. By this method, the olefinic protons of the dienes (384) and (385) shown below, were proven to be <u>trans</u>-orientated:-



(384)

δ7.9 [1H,d(J = 15 Hz), C_9-<u>H</u>];
δ6.3 [1H,d(J = 15 Hz), C_{10}-<u>H</u>] ppm

(385)

δ8.00 [1H,d(J = 16 Hz), C_9-<u>H</u>];
δ6.34 [1H,d(J = 16 Hz), C_{10}-<u>H</u>] ppm

A high value for the coupling constant (J = 15 or 16 Hz) is an indication of trans orientation of the olefinic protons.

5.2 Formation of suitable dienophiles

Initially, readily available dienophiles (See Figure 14) were used in order to investigate the scope and limitations of the Diels-Alder reaction. Having established the most favourable reaction conditions, several different types of suitable dienophiles (See Figures 15A and 15B) were synthesized, then employed as reactants. Some readily available aza-compounds (See Figure 16) were tested speculatively for potential dienophilic activity. Success having been achieved with maleic anhydride, led to the use of several analogues of maleic anhydride, (See Figure 17) as dienophiles.

Figure 14

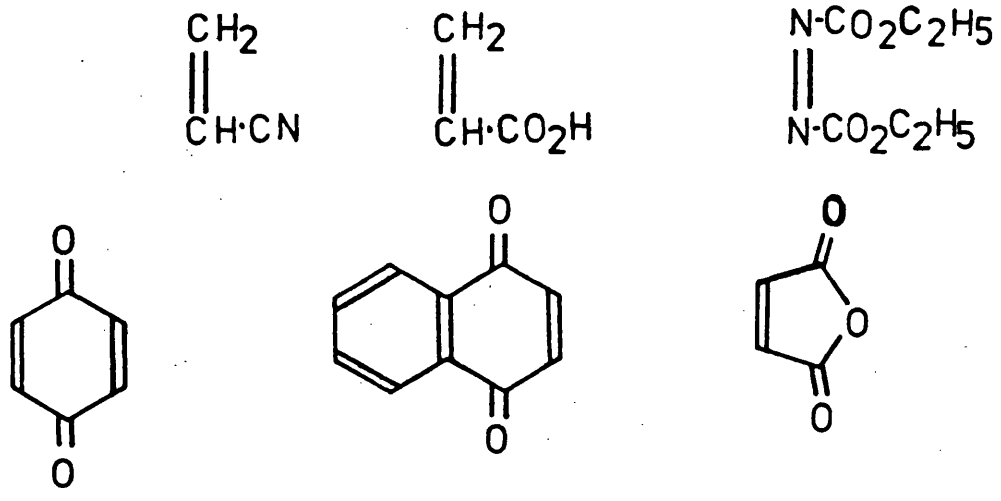


Figure 15A

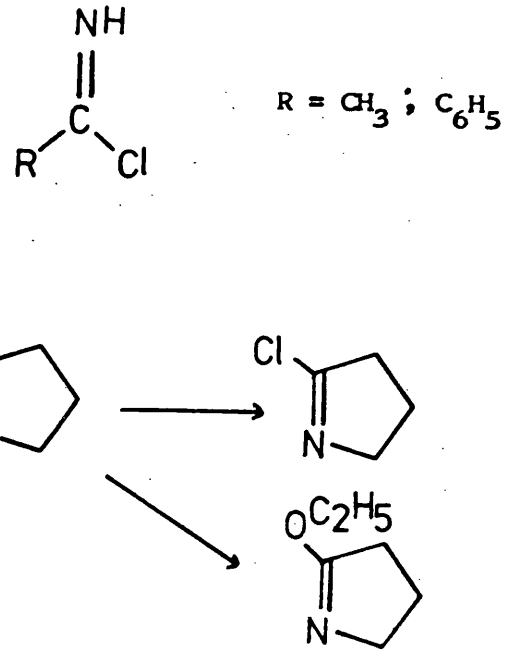


Figure 15B

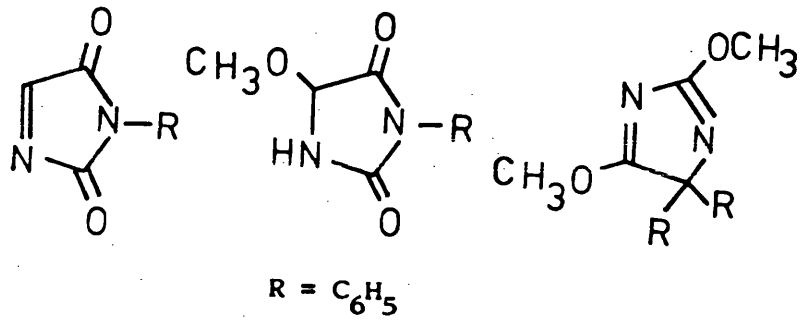


Figure 16

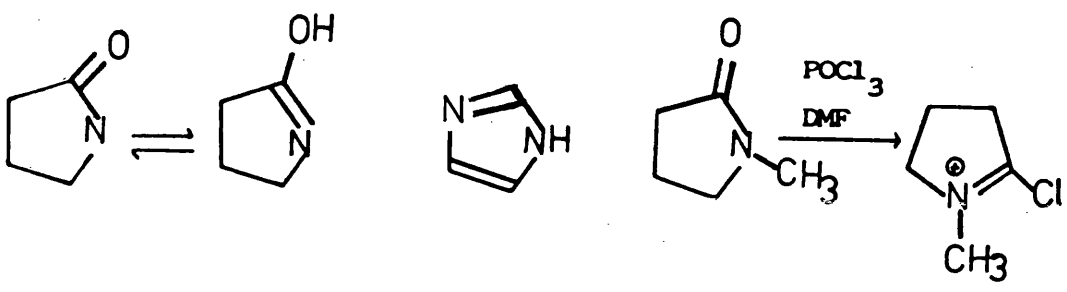


Figure 17

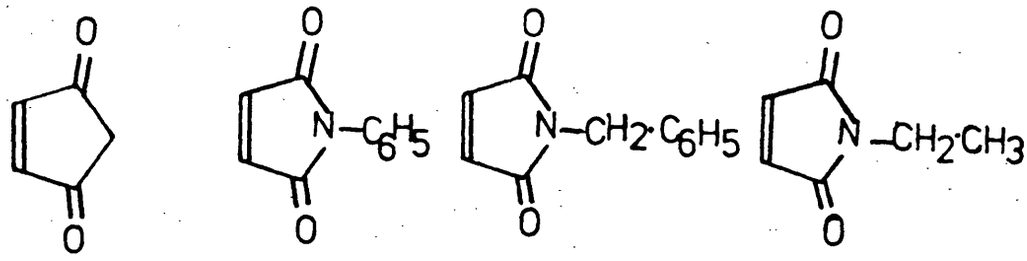
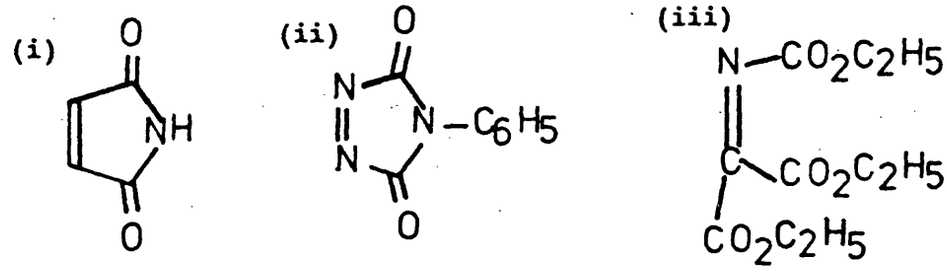


Figure 18



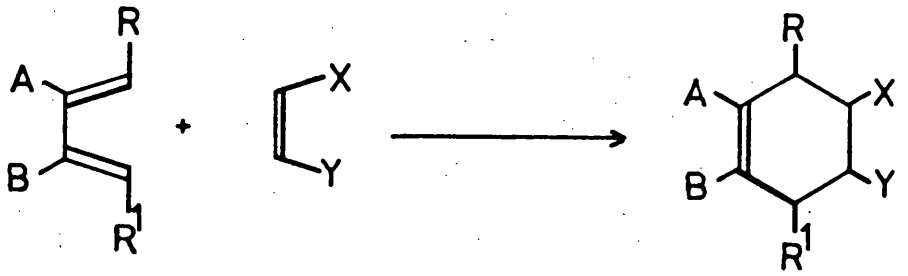
The mechanism of action and results of the above "dienophiles" will be discussed more fully in the relevant sections in Part 5.3.

5.3 The Diels-Alder Reaction

5.3.1 Introduction

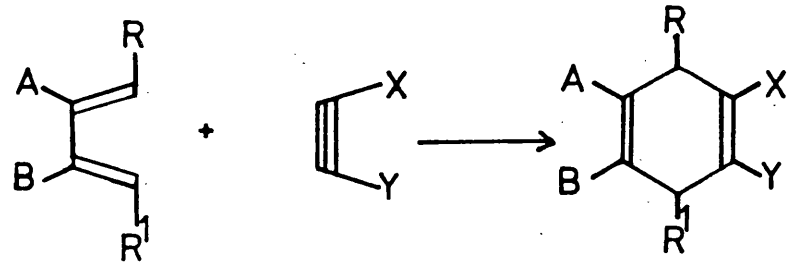
The Diels-Alder reaction, one example of a general class of cyclo-addition reactions, is one of the most useful synthetic reactions in organic chemistry. It involves the reaction of a 1,3 - diene in a 'cisoid' conformation[541] with an olefinic or acetylenic dienophile to form an adduct, containing a six-membered hydroaromatic ring (essentially a 1,4 - cycloaddition reaction):-

see overleaf:



A,B,R,R^1 - substituents on diene

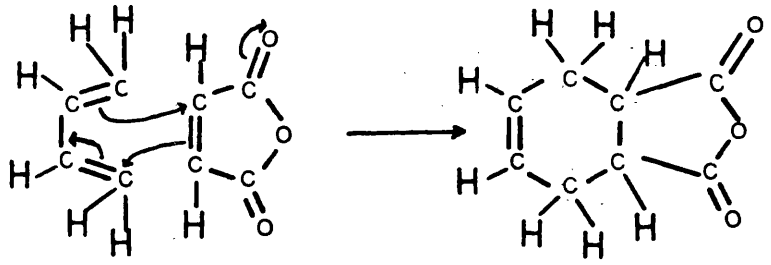
X,Y - substituents on dienophile



Two new sigma-bonds are formed in the product at the expense of two pi-bonds in the starting materials.[537] Many Diels-Alder reactions are accelerated by Lewis acid catalysts (aluminium chloride, boron trifluoride, stannic chloride etc.)[538-540] A typical Diels-Alder reaction involves an electron-rich diene and an electron-deficient dienophile. If a dienophile contains one or more activating substituents (electron withdrawing) (for example -CO-,-COOR, -C≡N, or $-NO_2$) in conjugation with a double or triple bond, it will react readily with a diene, αβ - Unsaturated carbonyl compounds (for example:- acrolein, acrylic acid and its esters, maleic acid and its anhydride, and acetylenedicarboxylic acid) are the most widely used dienophiles in organic synthesis on account of their enhanced activity towards dienes.

Many Diels-Alder reactions have been carried out with nitrogen - containing dienes and/or dienophiles. For further details, the reader is referred to the reviews by Hamer[542], Arbuzov[544], Needleman[545] and Cook[543].

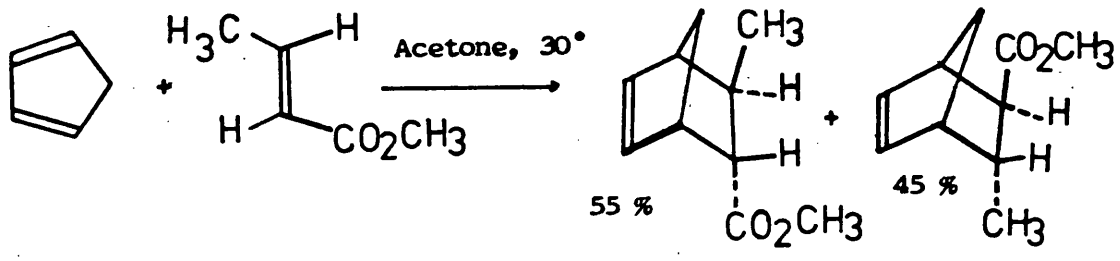
The Diels-Alder reaction may be expressed in terms of a cyclic flow of electrons,[546] without the necessity to postulate transient intermediate ions or radicals:-



5.3.2 Stereochemistry

In a Diels-Alder reaction, addition of the diene across the double bond of the dienophile is usually stereospecific, as exemplified by the reaction of methyl trans-crotonate with cyclopentadiene (See Figure 19).

Figure 19

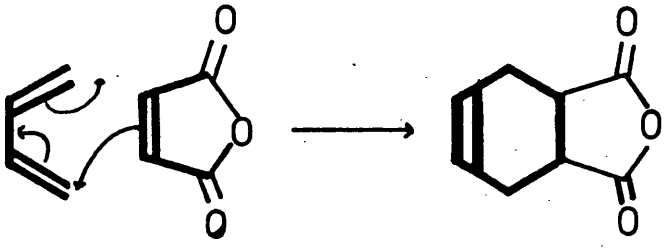


In both products, stereospecific addition has occurred across the crotonic ester bond i.e. the methyl and methyl-ester functionalities are trans. Addition to the double bond has therefore been cis (as usual). This implies that the addition is a concerted process and no free diradical intermediate capable of rotation about the newly formed single bond, is involved. Thus, for any Diels-Alder reaction, the relative stereochemistry of substituents in both the dienophile and the diene is retained in the resulting adduct.[547]

5.3.3 Mechanism of the Diels-Alder reaction

The mechanism of this reaction can be explained by the 'frontier orbital theory' employing the Woodward-Hoffmann rules for pericyclic reactions. The following explanation is given for a simplified Diels-Alder reaction i.e. reaction of butadiene with maleic anhydride or ethylene. However, this theory can be readily extended to explain the reactions occurring between more complex dienes and dienophiles used in this project.

Overall reaction:-



During the course of the reaction, two new sigma bonds are formed simultaneously, and the electrons mobilized in the reaction complete a circuit. Most pericyclic reactions are little influenced by Coulombic forces: for example, the polarity

of solvent has little or no effect on the rate of Diels-Alder reactions. The magnitude of interaction of the frontier orbitals of the reactants is the major factor influencing the rate of the reaction. For the simplified case, concerning unsubstituted reactants butadiene and ethylene, the former component has four pi-electrons and the latter two, and these are the only electrons involved in this [4 + 2] cycloaddition.

A cycloaddition reaction will occur, provided smooth bonding overlap can be achieved between the frontier orbitals as the reaction proceeds. For bonding overlap to occur (See Figure 20), two factors must be observed:-

1. A pair of frontier orbitals will overlap only if they are of like-sign (i.e. both positive or both negative).

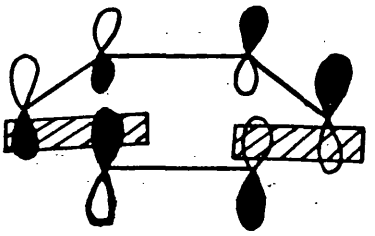
and 2. Geometrical structure of the molecule must be such that it enhances overlapping of frontier orbitals i.e. a "symmetry allowed" reaction in which the interaction of orbitals presents no energy barrier.

The Diels-Alder reaction shown in Figure 20 is classified as a [π4s + π2s] cycloaddition, since the two new sigma-bonds are formed on the same side (suprafacial) of the conjugated system. The overlapping of the frontier orbitals can proceed in either of two ways (A or B) (See Figure 20) for this case.

Figure 20

Overlap of the Frontier Orbitals of a Simple Diels-Alder Reaction

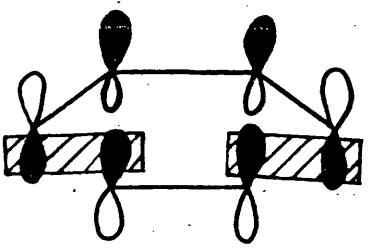
A.



HOMO of butadiene (Ψ_2).

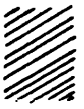
LUMO of ethylene (π^*).

B.



LUMO of butadiene (Ψ_3^*).

HOMO of ethylene (π).



development of bonding overlap as reaction proceeds.

N.B. Orbitals are not drawn to scale.

Frontier Orbitals: LUMO (unoccupied molecular orbital of lowest energy).

HOMO (Filled molecular obital of highest energy).

For further details the reader is referred to the excellent text by Fleming.[548]

5.3.4 Results

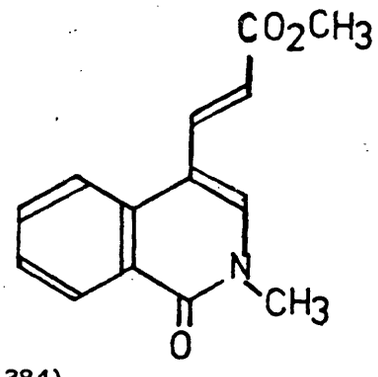
Many Diels-Alder reactions were carried out, some of which are shown in Tables 9 and 10, resulting in the formation of nitrogen-containing steroidal molecules. In some cases, a novel di-adduct formation was observed.

General procedure:-

To the diene (1 equivalent) dissolved in acetonitrile, the dienophile (1-4 equivalents) was added. The resulting solution was heated under reflux (12 - 72h). After cooling the mother liquor, the precipitated product (in most cases) was isolated by filtration, then recrystallized from a suitable solvent to afford a pure sample of the adduct.

Table 9

Adducts formed by employing the methyl ester (384) as diene.



(384)

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Table 9

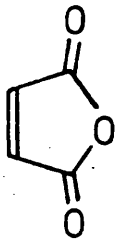
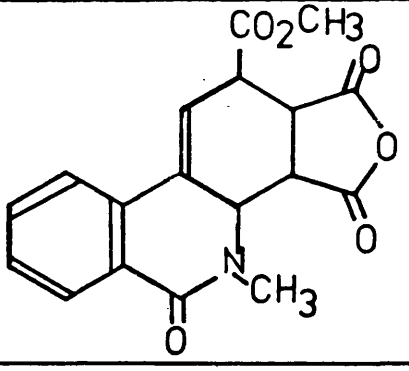
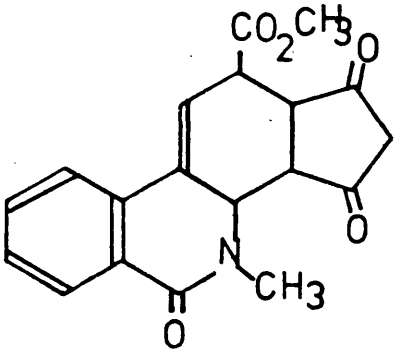
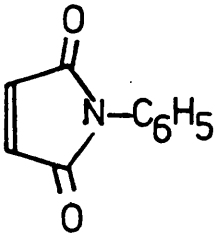
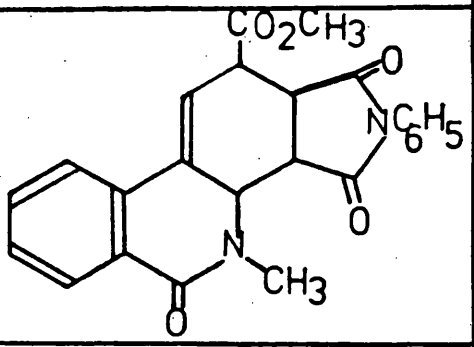
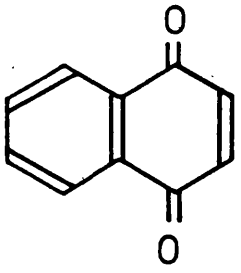
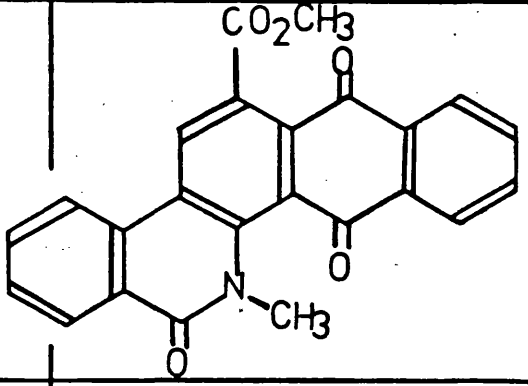
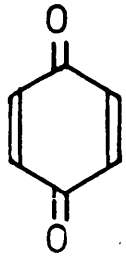
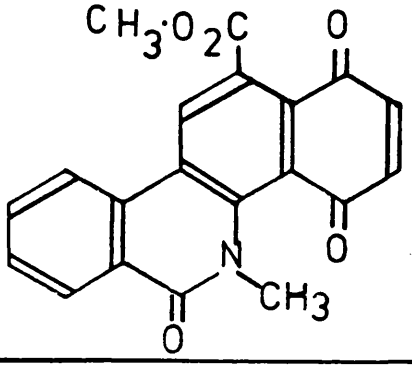
Dienophile employed	Resulting Adduct	M.P.	% yield	Product No.
		244-246°	91%	(399)
		254-255°	91%	(400)
		259-260°	86%	(401)
		302-305°	90%	(403)
		259°	43%	(402)

Table 9 (continued)

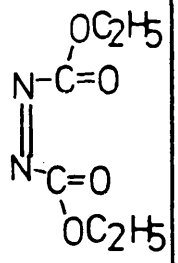
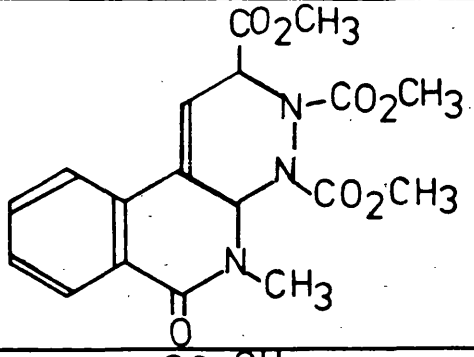
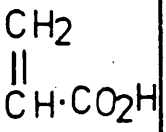
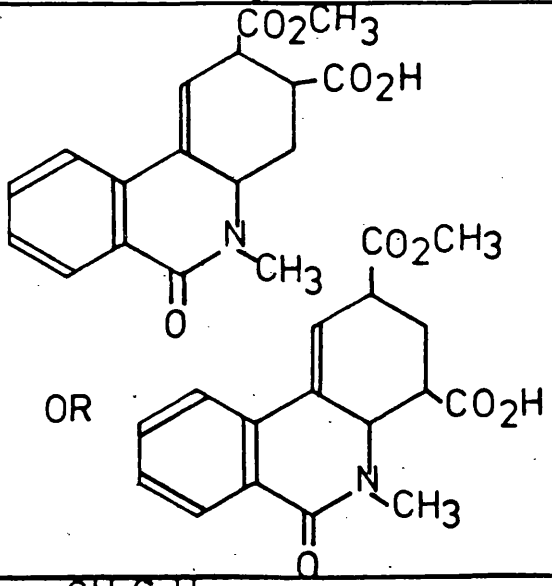
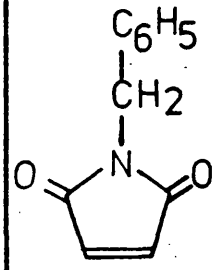
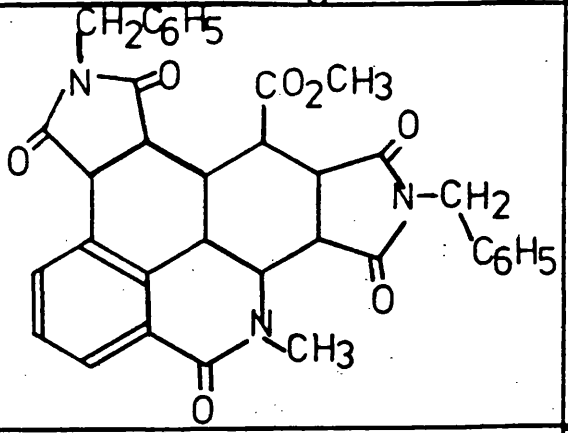
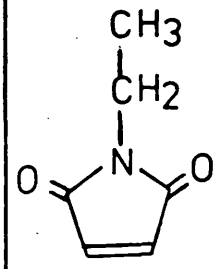
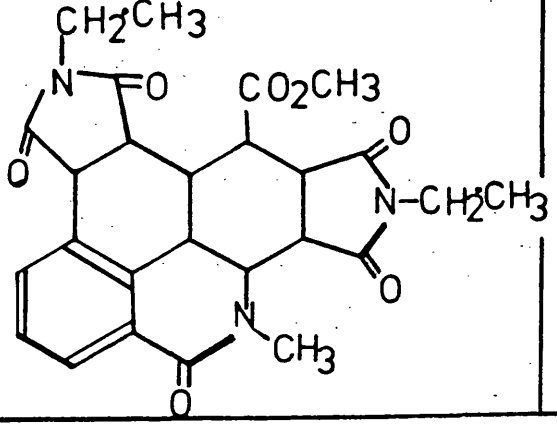
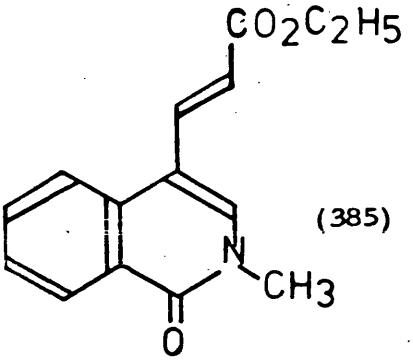
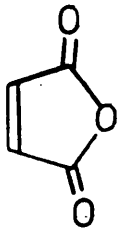
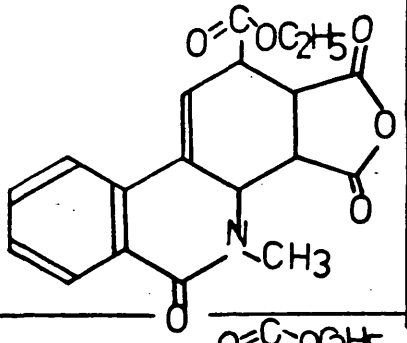
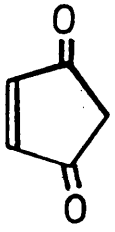
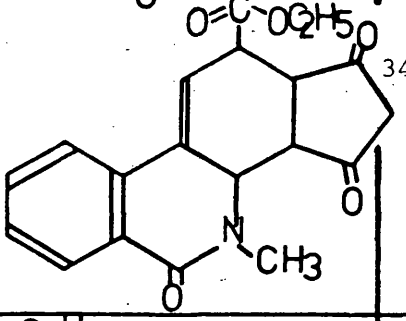
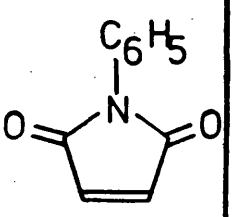
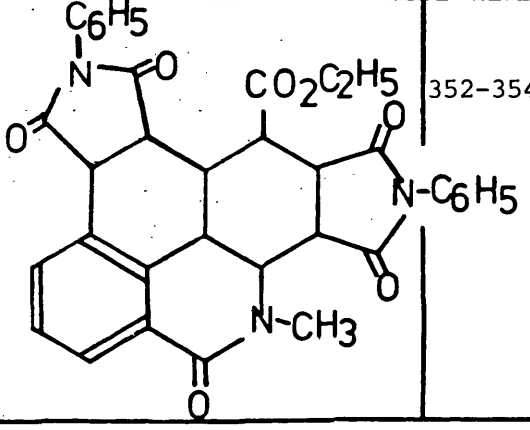
Dienophile employed	Resulting Adduct	M.P.	% yield	Product No.
		164-168°	<10%	(404)
		223-225°	82%	(398)
		314-315°	58%	(405)
		340°	61%	(408)

Table 10

Adducts formed by employing the ethyl ester (385) as diene.



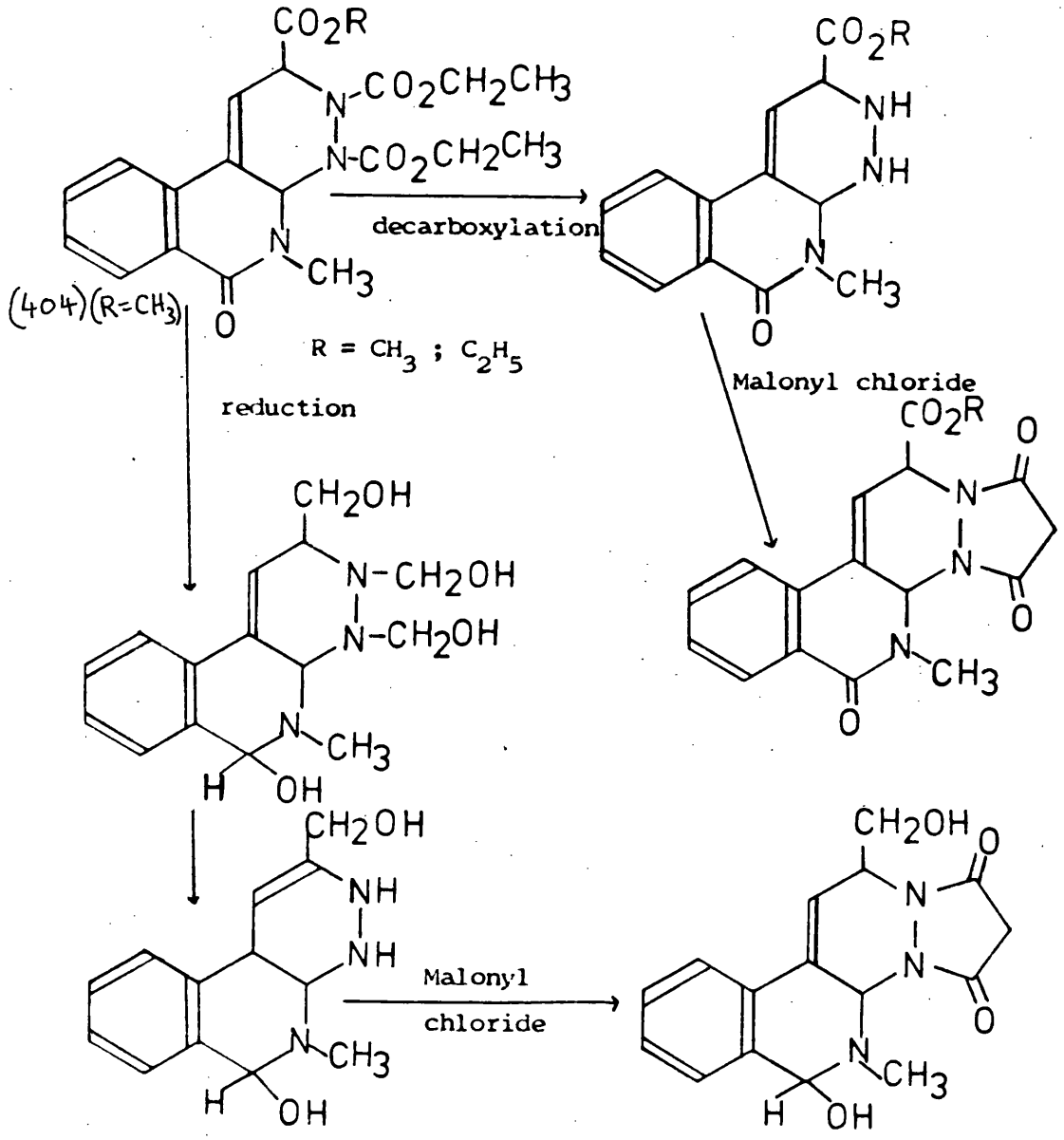
(385)

Dienophile employed	Resulting Adduct	M.P.	% yield	Product No.
		239-240°	83%	(410)
		348-350°	74%	(411)
		352-354°	35%	(412)

5.3.5 Adduct Formation

Work by Gillis et al.[549,550] and Franzus et al.[551] suggested the feasibility of employing diethyl azodicarboxylate as a dienophile. Reaction of the diene (384) with diethyl azodicarboxylate furnished the adduct (404), but unfortunately in poor isolable yields, which could not be improved upon. If the yields had been high, this reaction may have presented a synthetic route (see Scheme 39) to 'azasteroids' containing the "N-C-N" moiety, required for pharmacological evaluation in this project.

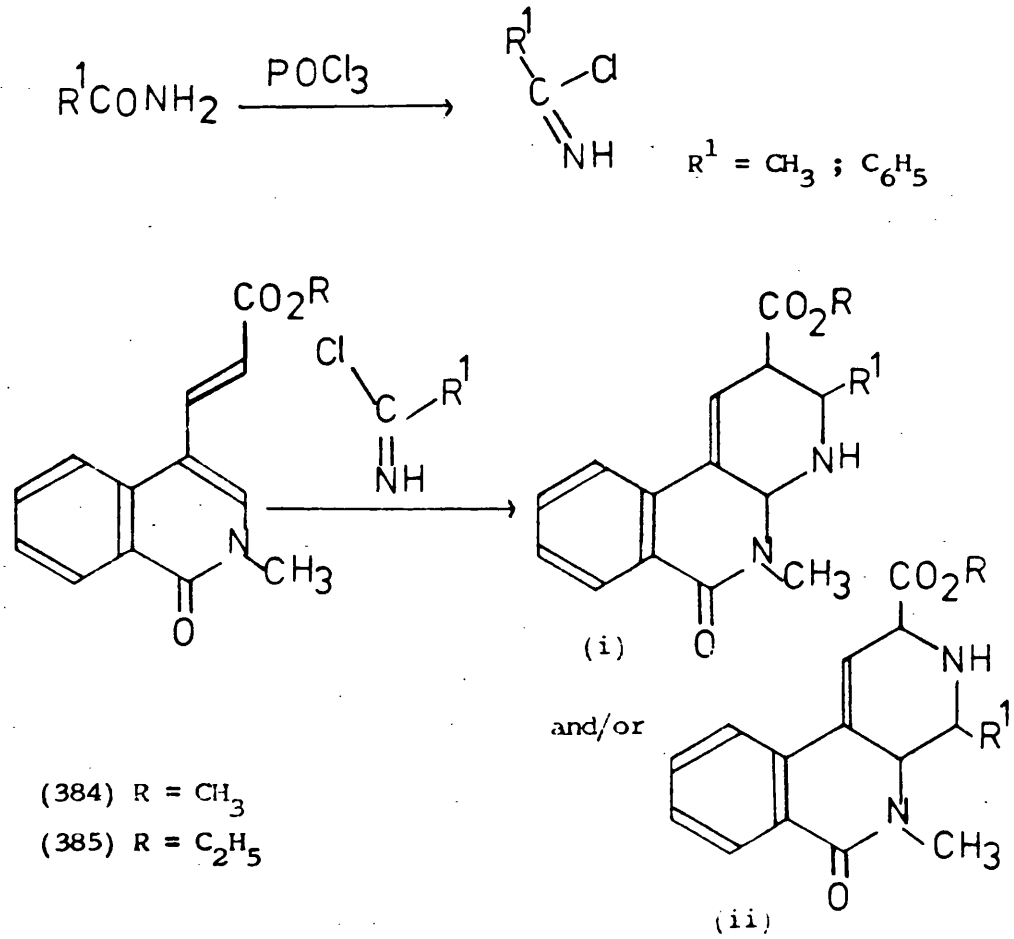
Scheme 39



It may also be possible to prepare 'azasteroids' containing the "N-C-N" moiety *via* the use of dienophiles (ii)[552,553] and (iii)[554] shown in Figure 18. In fact, 4-phenyl-1,2,4-triazoline-3,5-dione (ii) (Figure 18) is a better dienophile than *N*-phenyl maleimide.[556]

Imidoyl chlorides[555] were prepared then reacted with dienes (384) and (385) in an attempt to obtain adducts of type (i) and (ii) (See Figure 21).

Figure 21

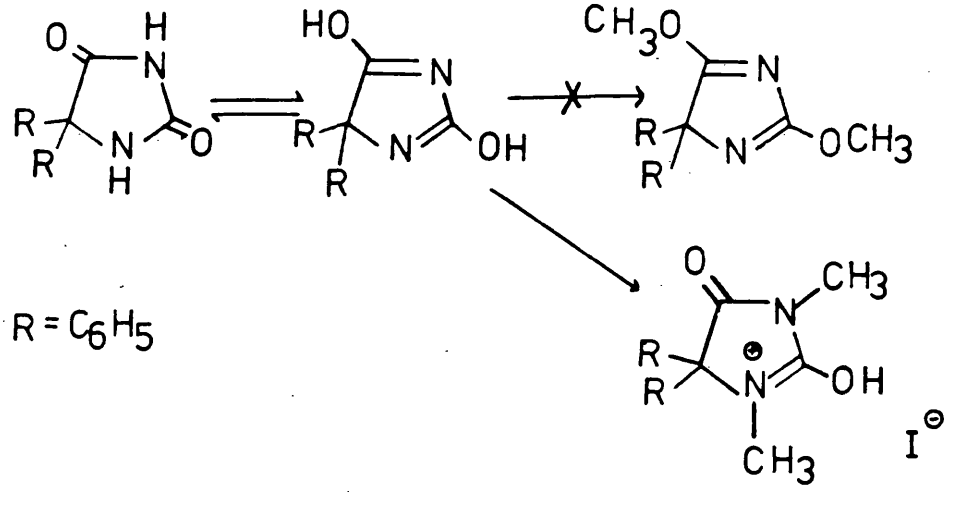


After several attempts during which, either starting material [(384) or (385)] or decomposed products were recovered, this synthetic route was abandoned.

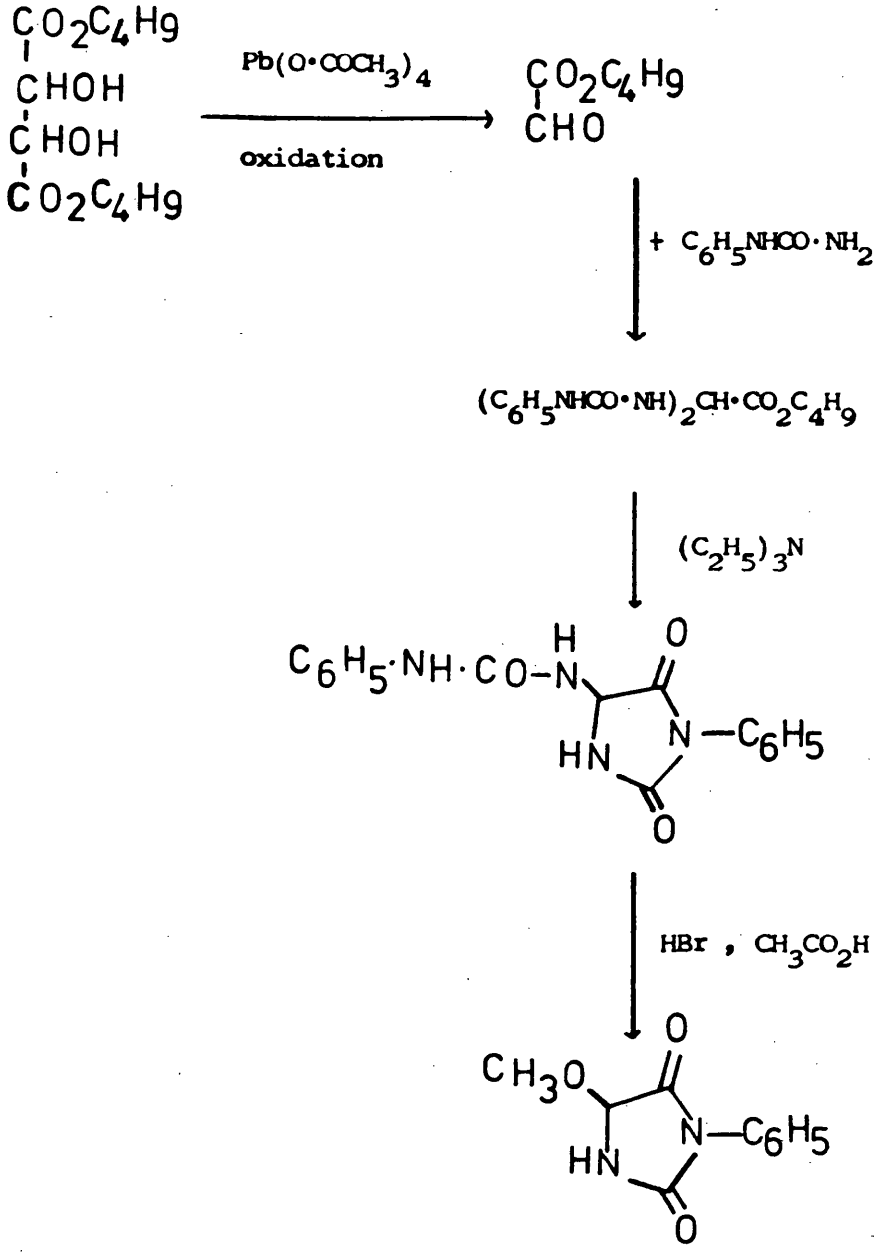
A mathematical treatment of molecular orbitals and electron density considerations[548] (if adequate physical data available), may be used to postulate the orientation of the cycloaddition resulting in products (i) or (ii) (See Figure 21).

Goldstein et al.[556,557] and Evnin et al.[558] reported the successful use of hydantoins as dienophiles in Diels-Alder reactions. This prompted an investigation of hydantoins as potential dienophiles in this project. However, preparative methods leading to the hydantoins shown in Figure 15B were either too lengthy or unsuccessful (See Schemes 40 and 41), therefore this approach to potentially useful adducts was abandoned.

Scheme 40



Scheme 41

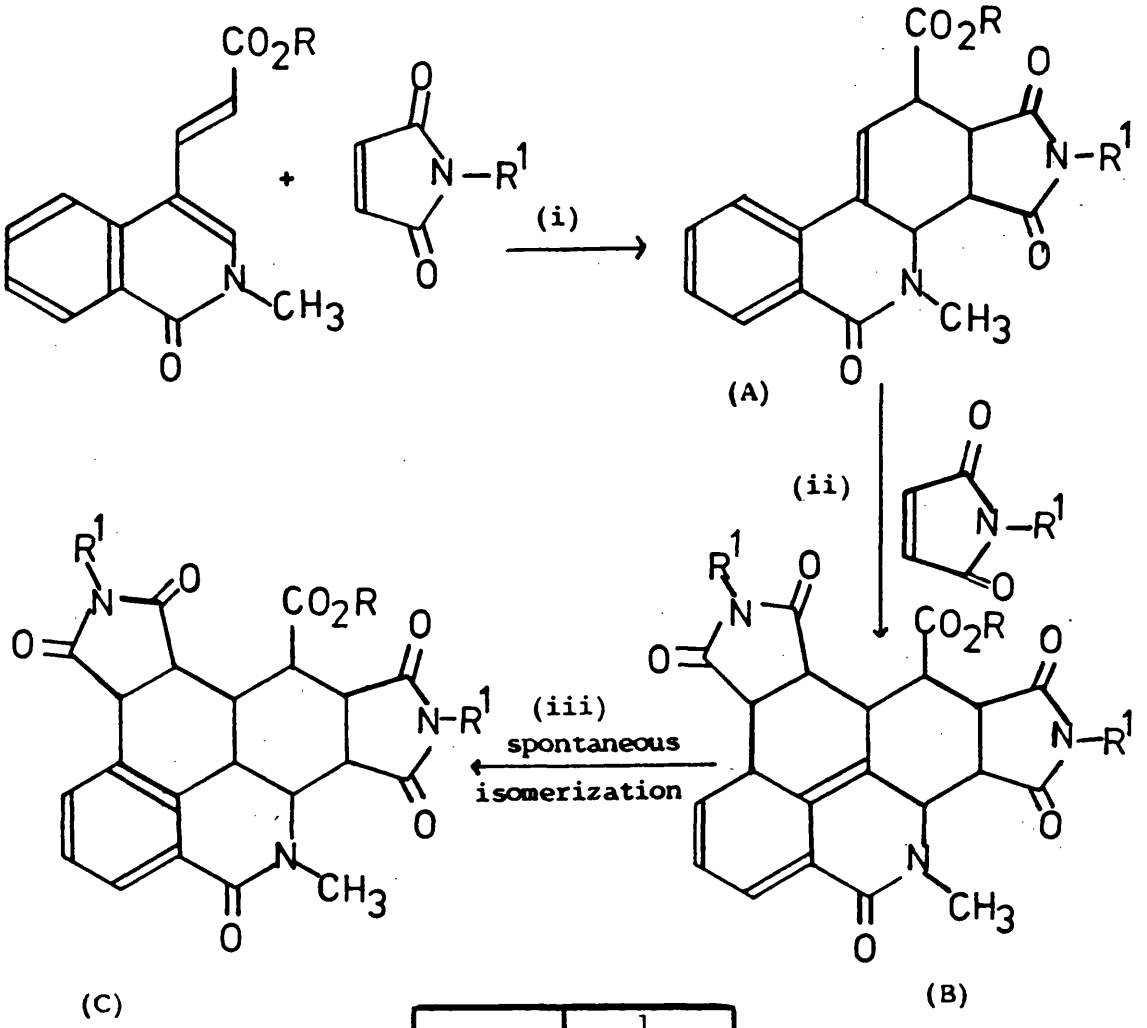


5.3.6 Di-adduct formation

In some of the Diels-Alder reactions carried out, an unusual di-adduct formation was observed. However, in the cases where a di-adduct was the isolated product, the mono-adduct could not be synthesized even if a 1:1 equivalent of reactants was employed. This suggested that the two stages of the double Diels-Alder reaction occur simultaneously, i.e. as the new diene forms, it reacts immediately with a further molecule of

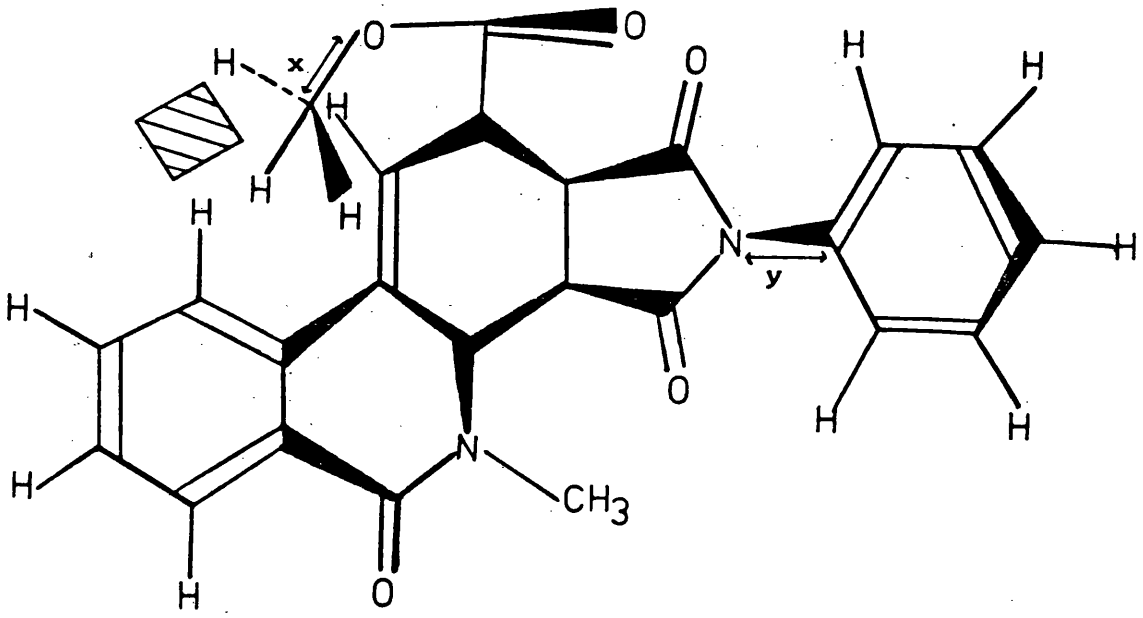
the dienophile (See Scheme 42).

Scheme 42



R	R^1
CH_3	CH_2CH_3
CH_3	$CH_2C_6H_5$
C_2H_5	C_6H_5

Diagram 1



Provided distances x and/or y are sufficiently large, the ester function or phenyl group behave as a "claw" to hold the second dienophile (▨) in position, thus enabling the reaction to proceed.

Step (i) shown in Scheme 42 is the rate-determining step, indicated by the fact that the mono-adduct (A) formed in each case, was not isolable. The mechanism for this reaction is not known, but examination of the stereochemistry employing "Dreiding" models (See Diagram 1), suggests that the spatial arrangement of the atoms in the mono-adduct (A) influences the addition of a second molecule of the dienophile to yield the di-adduct (B). Intermediate (B) readily isomerizes to afford the more stable final product (C).

Several unsuccessful attempts were made to introduce a different second dienophile to the mono-adduct (A), (See

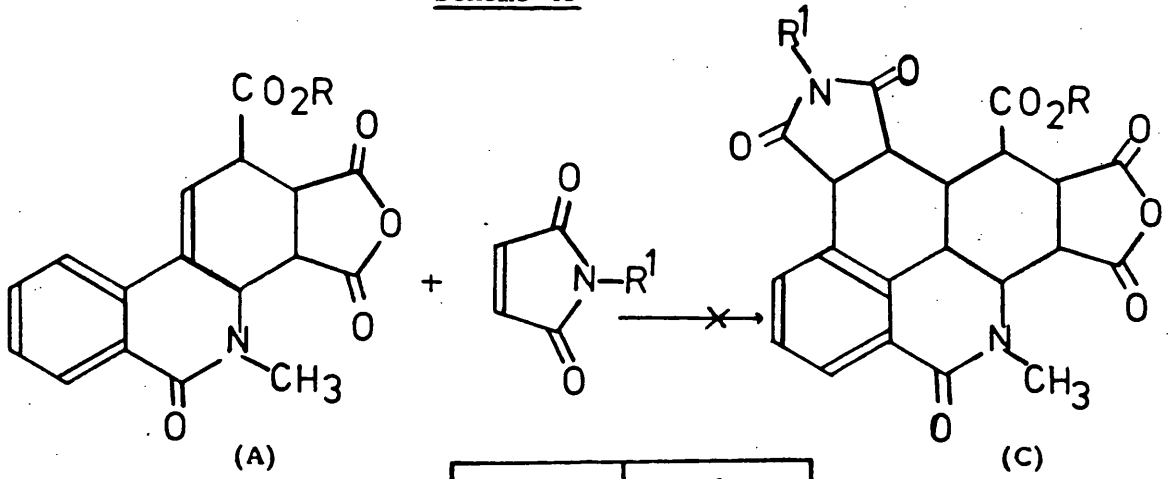
Schemes 43 and 44). These may have failed due to one of two factors:-

1) Unfavourable reaction as dictated by the Woodward-Hoffmann rules for pericyclic reactions (see Section 5.3.3).

2) Mono-adduct (A), (Schemes 43 and 44), is not sufficiently soluble in solvent employed, for reaction to occur.

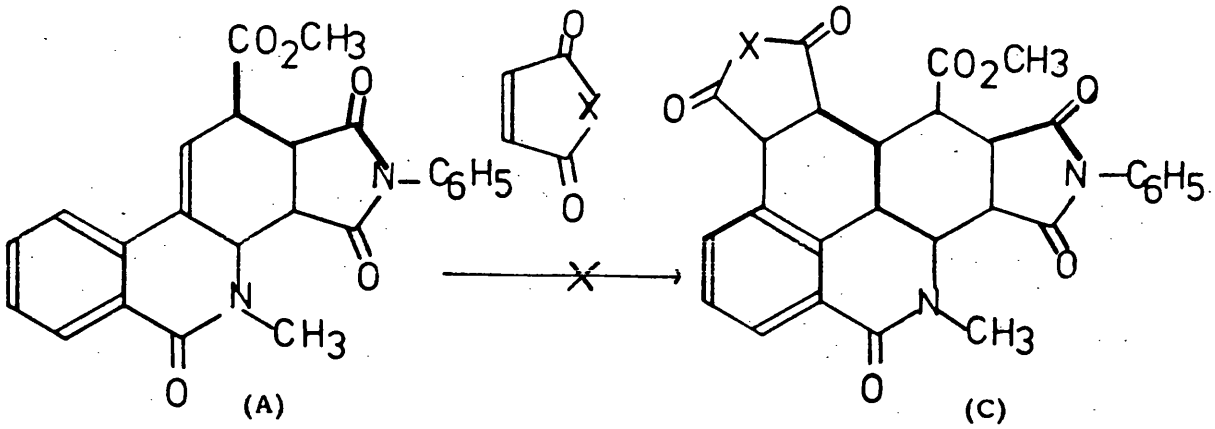
Reactions shown in Schemes 43 and 44 were carried out as suspensions in acetonitrile. When attempted in tetrahydrofuran (THF), N,N-dimethylformamide(DMF), or dimethyl sulphoxide (DMSO), decomposition of the mono-adduct (A) resulted. Owing to solubility problems encountered, the results are not conclusive.

Scheme 43



R	R^1
CH_3	C_6H_5
C_2H_5	C_6H_5
CH_3	$CH_2C_6H_5$
C_2H_5	$CH_2C_6H_5$
CH_3	CH_2CH_3
C_2H_5	CH_2CH_3

Scheme 44

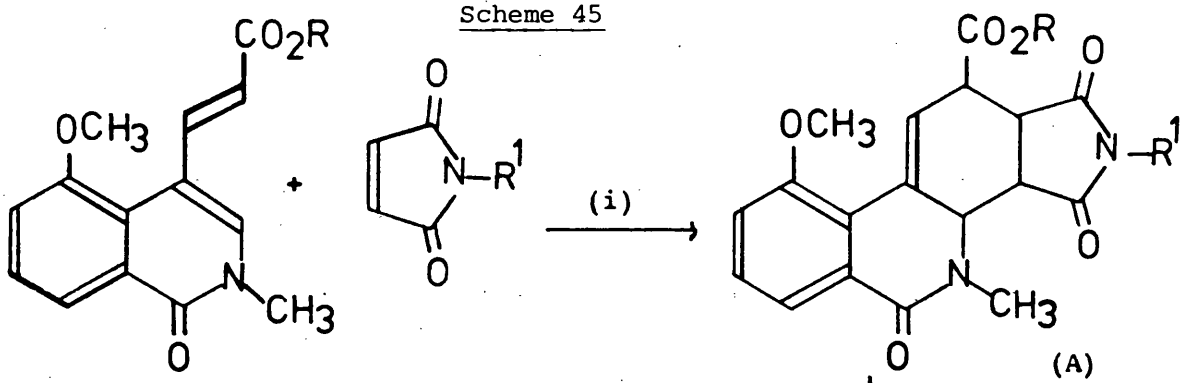


(A) (C)

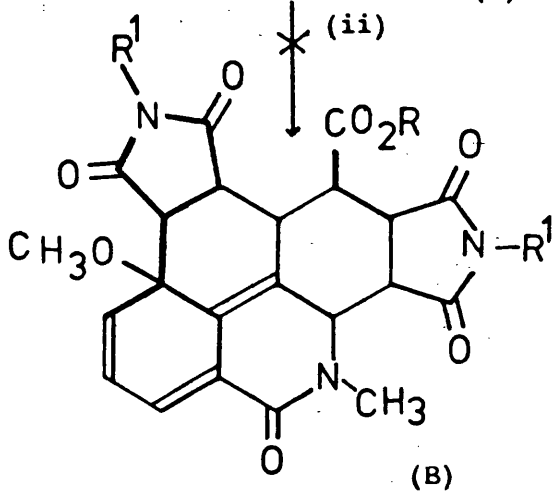
X = >O ; >N-CH_2CH_3 ; >N-$CH_2C_6H_5$

Since no mono-adduct (A) could be isolated from the reactions shown in Scheme 42, it may be interesting to examine the possibility of mono-adduct formation by employing a diene with a sterically hindered position 5 so as to render stage (ii) (Scheme 42) unfeasible. Steric hindrance may be caused by the introduction of a methoxy, phenyl, or phenoxy function at position 5 of the diene (see Scheme 45).

Scheme 45



(A)

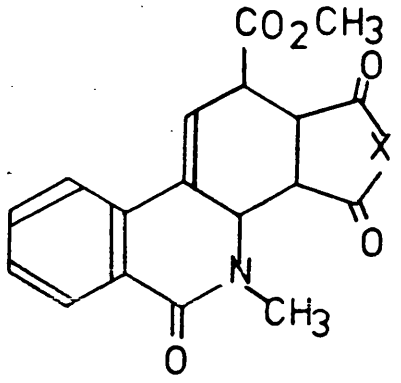


(B)

R	R^1
CH_3	CH_2CH_3
CH_3	$CH_2C_6H_5$
C_2H_5	C_6H_5

5.4 Reduction of Adducts (399) and (401)

Several reducing agents[561-563] were employed in attempts to selectively reduce adducts (399) and (401), in order to investigate the chemistry of these adducts and also to obtain potentially useful samples for biological testing.



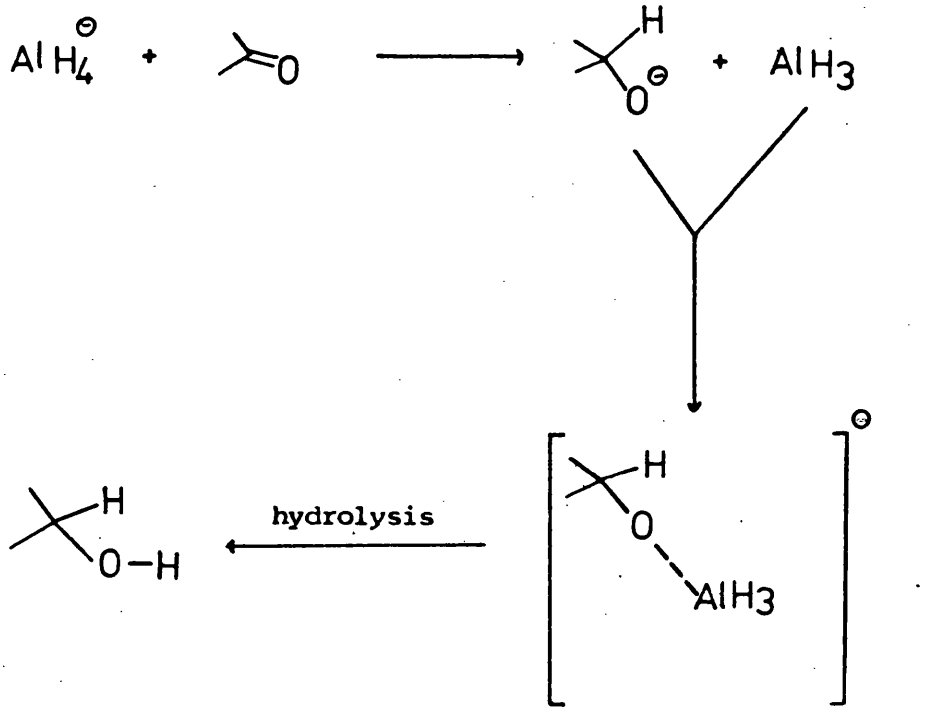
(399) X = >O

(401) X = >N-C_6H_5

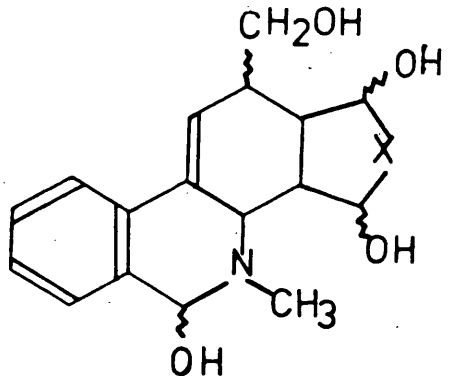
5.4.1 Lithium Aluminium Hydride ($LiAlH_4$)[559] is a powerful reducing agent for a wide range of organic compounds. It is known for its ability to reduce the carbonyl functionality in compounds such as esters, ketones, amides etc.

In ether solutions, $LiAlH_4$ is postulated to exist largely as ionic aggregates of strongly solvated lithium ions and aluminohydride anions ($AlH_4^{\ominus}$). Most normal reduction reactions involve the displacement of a strongly electronegative atom (oxygen, nitrogen, or halogen) and the addition of a hydrogen atom to the electron-deficient centre (usually a carbon atom). Hydrogen is transferred from the reactive species (aluminohydride anion) as the hydride ion, in a bimolecular nucleophilic displacement type mechanism. A possible mechanism for the reduction of ketones is outlined in Scheme 46.

Scheme 46



Theoretically, the reduction of adduct (399) or (401) with $LiAlH_4$ was expected to yield one product which may be present as one or more stereoisomers i.e.



However, experimentally it was found that several reduced products resulted, which could not be isolated satisfactorily owing to their extremely insoluble nature. Attempted separation by column chromatography and preparative thin-layer chromatography resulted in decomposition of products.

5.4.2 Sodium borohydride ($NaBH_4$) which is not as powerful a reducing agent as $LiAlH_4$, was then employed in attempts to reduce the adducts (399) and (401) more selectively. Although three modified conditions were tried, each attempt resulted in a mixture of reduced products.

Modifications attempted:-

a) $NaBH_4$/ethanol

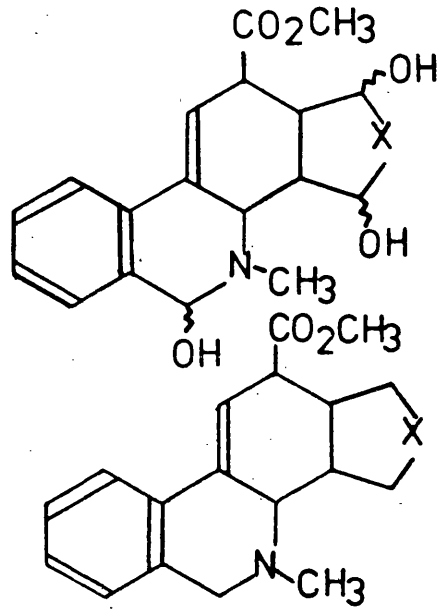
b) $NaBH_4$/methanol/ethanol

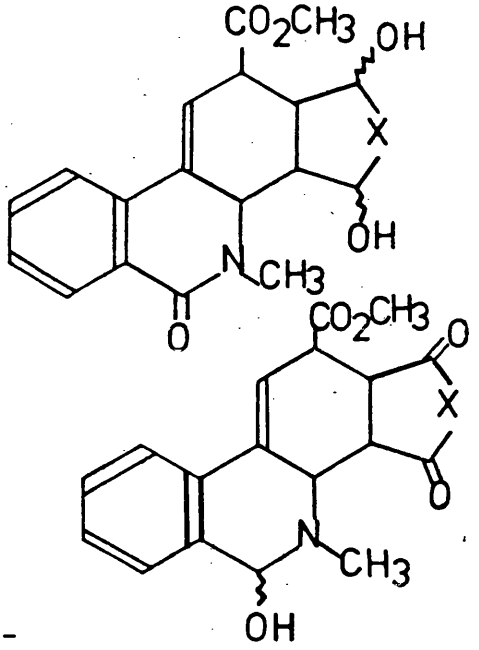
c) $NaBH_4$/acetic acid[560]

Owing to the complexity of the adducts (399) and (401), attempts to reduce them can lead to several different products (some of which are shown in Figure 22.). One final, fully reduced product could not be obtained even though greatly modified and varied reaction conditions were employed.

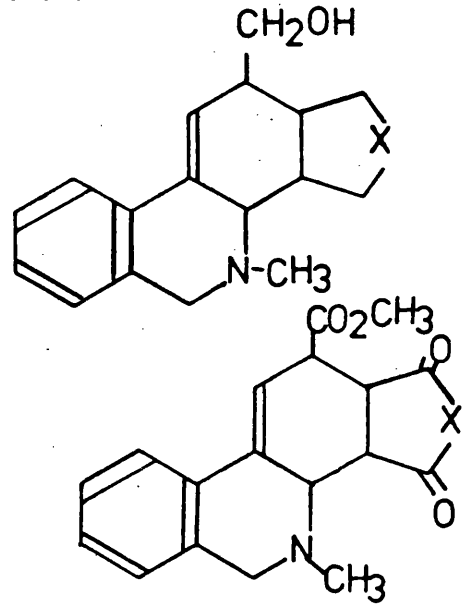
Figure 22

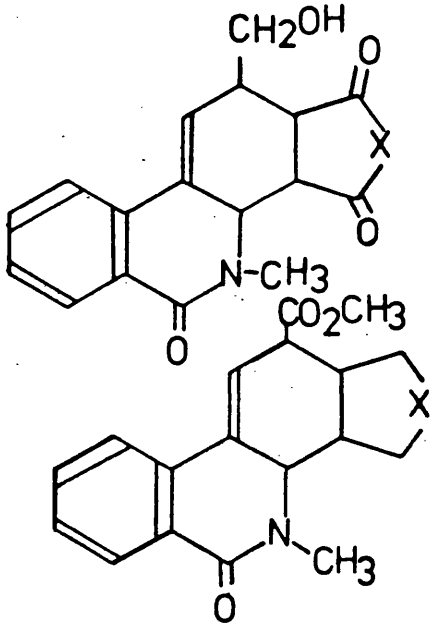
via $NaBH_4/C_2H_5OH$ reduction:-

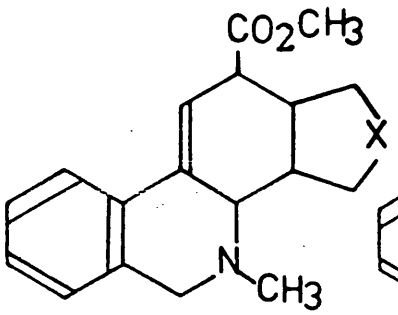


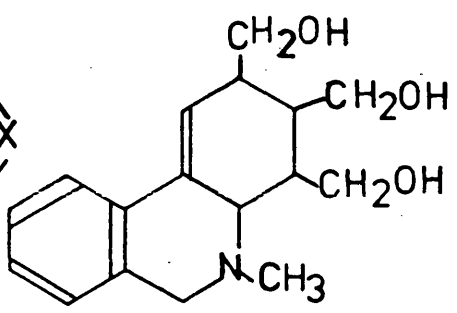


via $NaBH_4/C_2H_5OH/CH_3OH$ reduction:-









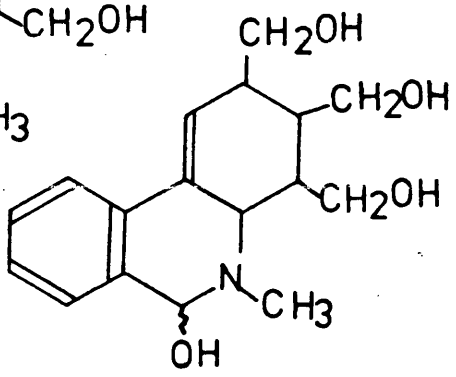
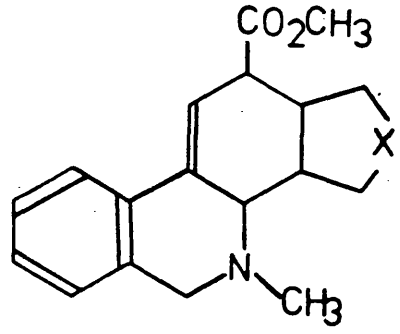
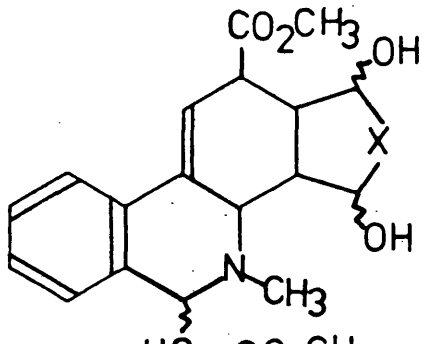
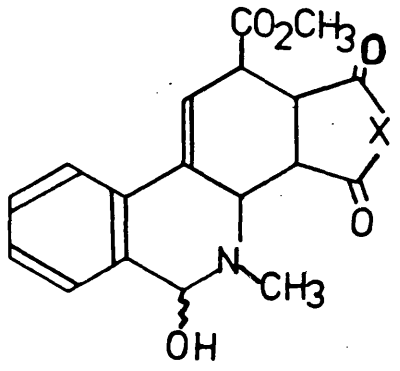
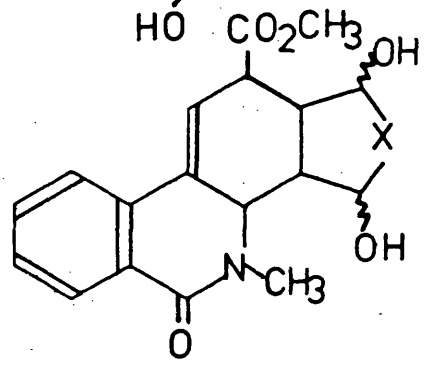
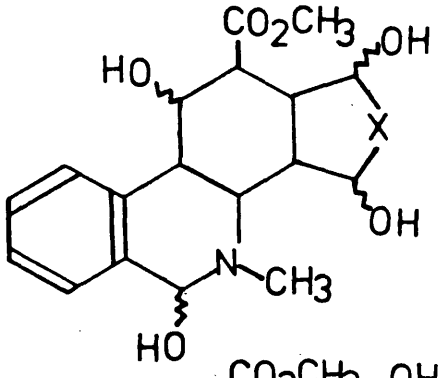
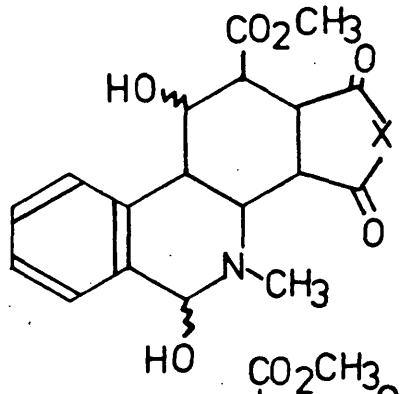
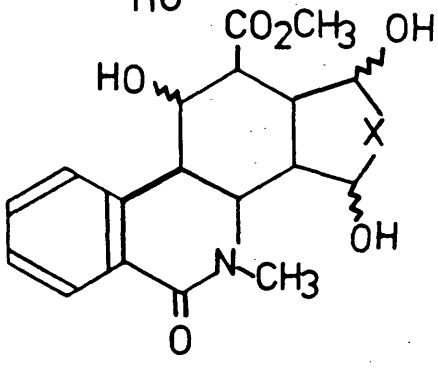
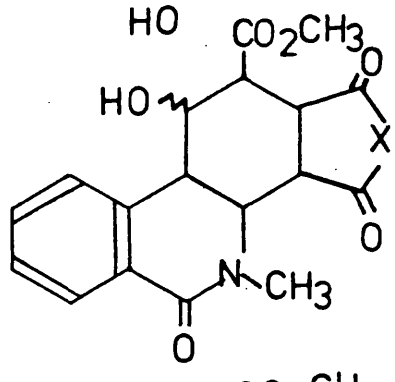
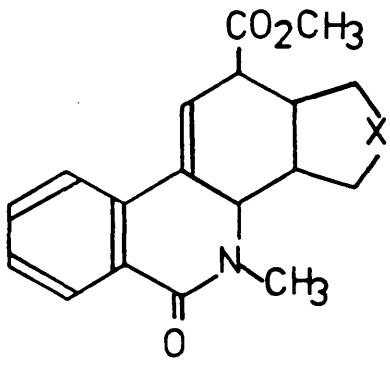
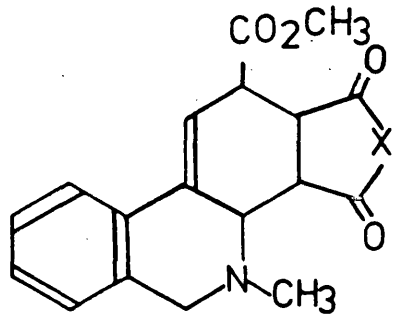


Figure 22 (continued)

via $NaBH_4/CH_3CO_2H$ reduction:-

via B_2H_6-THF reduction:-

5.4.3 Attempts to reduce selectively the adducts (399) and (401) were also made with diborane,[564-566] and again a complex mixture of reduced products was obtained each time (see Figure 22).

These adducts could not be reduced successfully to one product owing to several factors:-

i) Complex nature of adducts. Adducts contain several reducible functionalities.

ii) Adducts are extremely insoluble in most solvents, but in other solvents (e.g. THF, DMSO etc.) they undergo decomposition readily.

iii) If reducing conditions employed are too harsh, then complete decomposition of starting material and/or reduced products occurs.

iv) The 'work-up' procedures necessary at the termination of some reduction reactions (especially those involving hydroboration) to cleave the carbon-boron bond in order to release the free reduced product, are sometimes so harsh (e.g. alkaline hydrogen peroxide) that decomposition of the reduced products occurs rapidly.

Some success was achieved when diborane was employed as a reducing agent i.e. only four-seven products resulted.

PART II RESULTS AND DISCUSSION (CONTINUED)

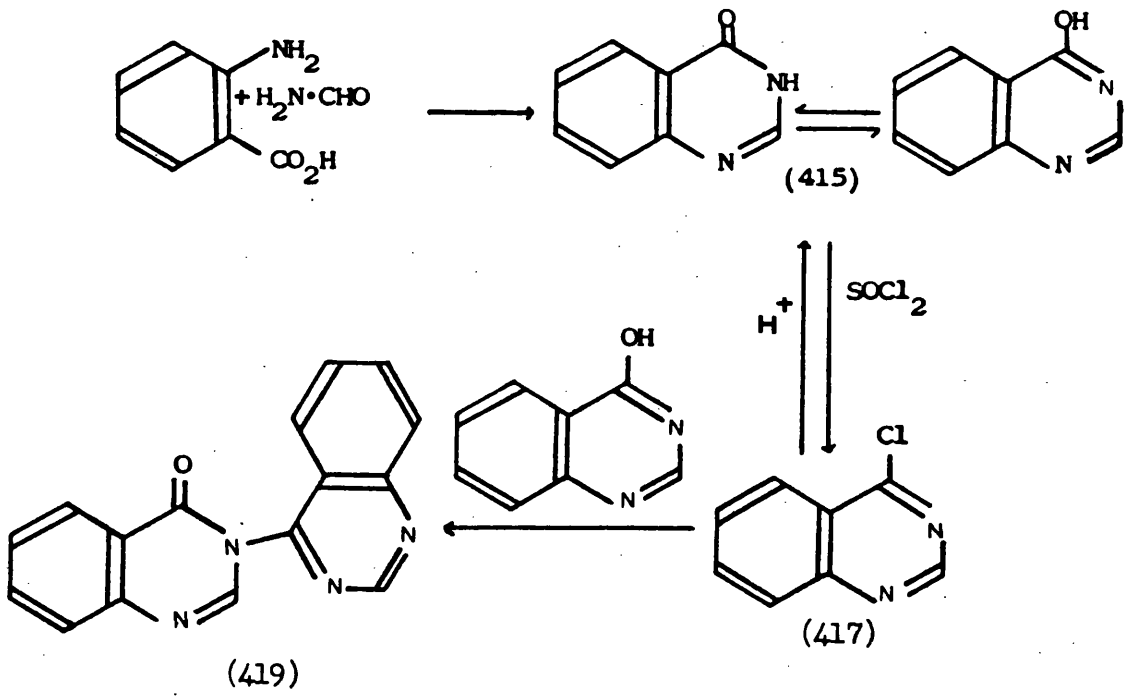
C H A P T E R S I X

SYNTHESIS OF DI- AND TRI-AZASTEROID INTERMEDIATES FROM 4-SUBSTITUTED QUINAZOLINES

6.1 4-Chloroquinazoline (417) (see Scheme 47) and 4-aminoquinazoline (443) (see Scheme 48)[520] were employed as starting materials.

6.1.1 4-Hydroxyquinazoline (415) is obtained readily in yields of >95% by the condensation of anthranilic acid with formamide. Absorption peaks at $\nu_{max.}$ 3,200 cm^{-1} and 1,700 cm^{-1} in the infra-red spectrum of (415) confirmed the presence of a hydroxy and a carbonyl functionality, respectively.

Scheme 47

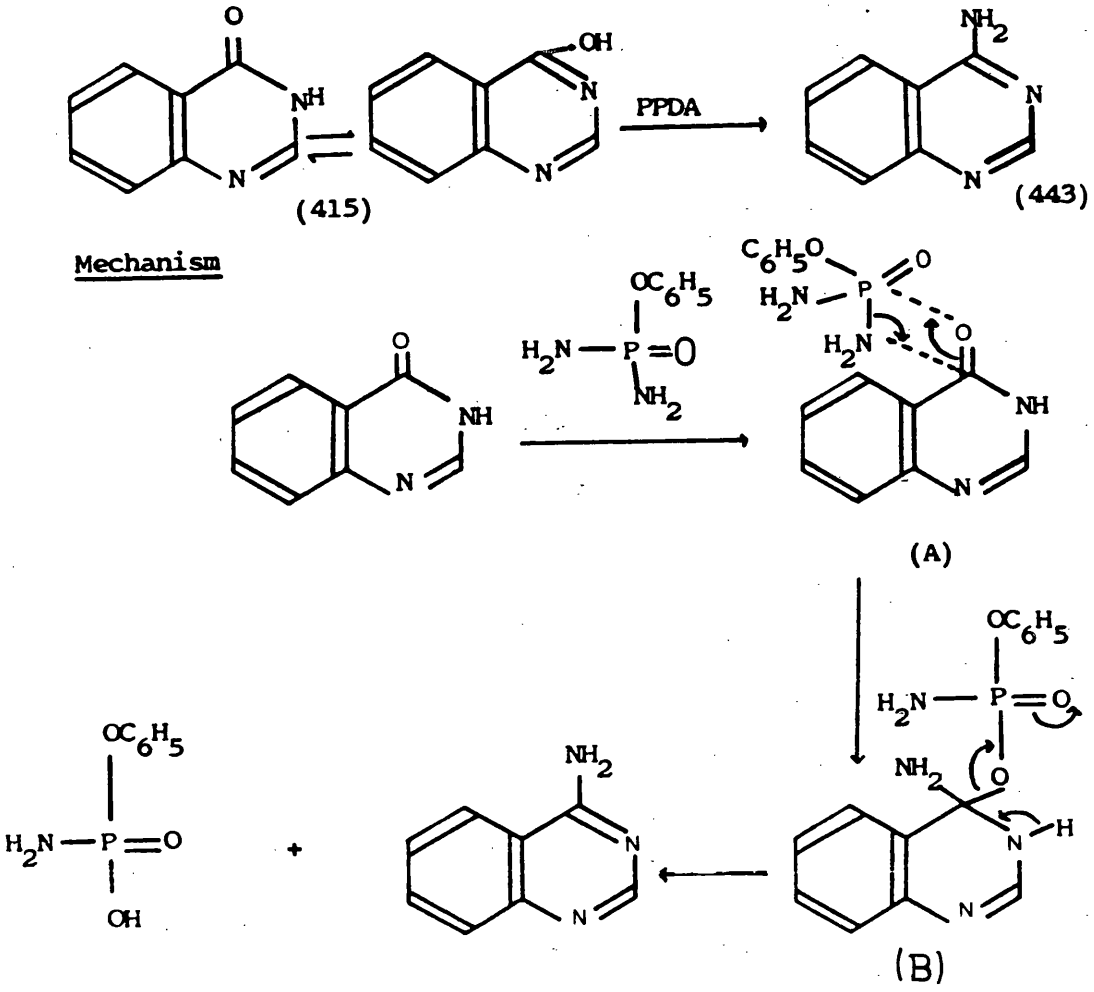


Treatment of 4-hydroxyquinazoline (415) with thionyl chloride (freshly distilled from linseed oil) afforded 4-choroquinazoline (417), in 80% yield, which was found to be extremely unstable. In presence of acid, 4-chloroquinazoline readily undergoes hydrolysis to give 4-hydroxyquinazoline (415), and in the presence of trace amounts of 4-hydroxyquinazoline, 4-chloroquinazoline undergoes "dimerization" to give the "dimer" (419). Purification of 4-chloroquinazoline was achieved by passing the crude material through an alumina column.
The molecular ion observed at m/e 164 by mass spectrometry supports structure (417). The PMR spectrum shows four aromatic protons resonating at δ7.7 - 8.4 ppm and the C_2 - aromatic proton downfield at δ9.2 ppm.

6.1.2 4-Aminoquinazoline (443) was prepared in yields of >68%, by the reaction of 4-hydroxyquinazoline (415) with phenyl phosphorodiamidate (PPDA).[520] The PMR spectrum obtained for product (443) showed the five aromatic protons appearing together as a multiplet at δ7.2 - 8.5 ppm, and the two protons of the amino functionality as a broad peak at δ4.6 - 6.0 ppm. Mass spectral evidence (molecular ion at m/e 145) also supported this structure for product (443).

A possible mechanism for this amination is outlined in Scheme 48. The reaction has been proposed by Rosowsky et al.[520] to involve the transition states [A] and [B] (Scheme 48). The free energy gain associated with formation of a new P-O bond and rupture of a P-N bond is high enough to drive the reaction to completion.

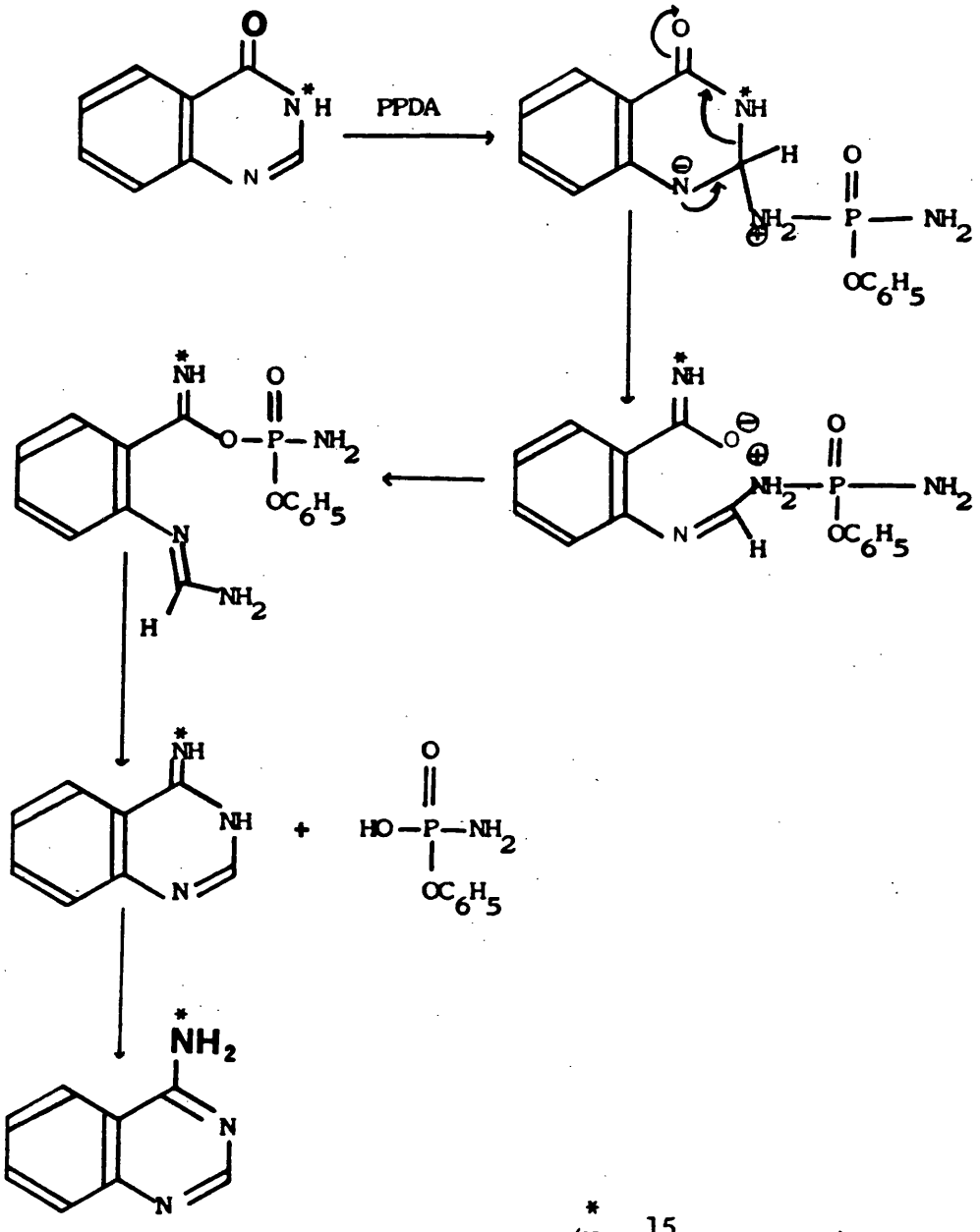
Scheme 48[520]



An alternative mechanism, involving ring-opening and ring-closure, has been proposed by Kroon and Plas,[567] (see Scheme 49).

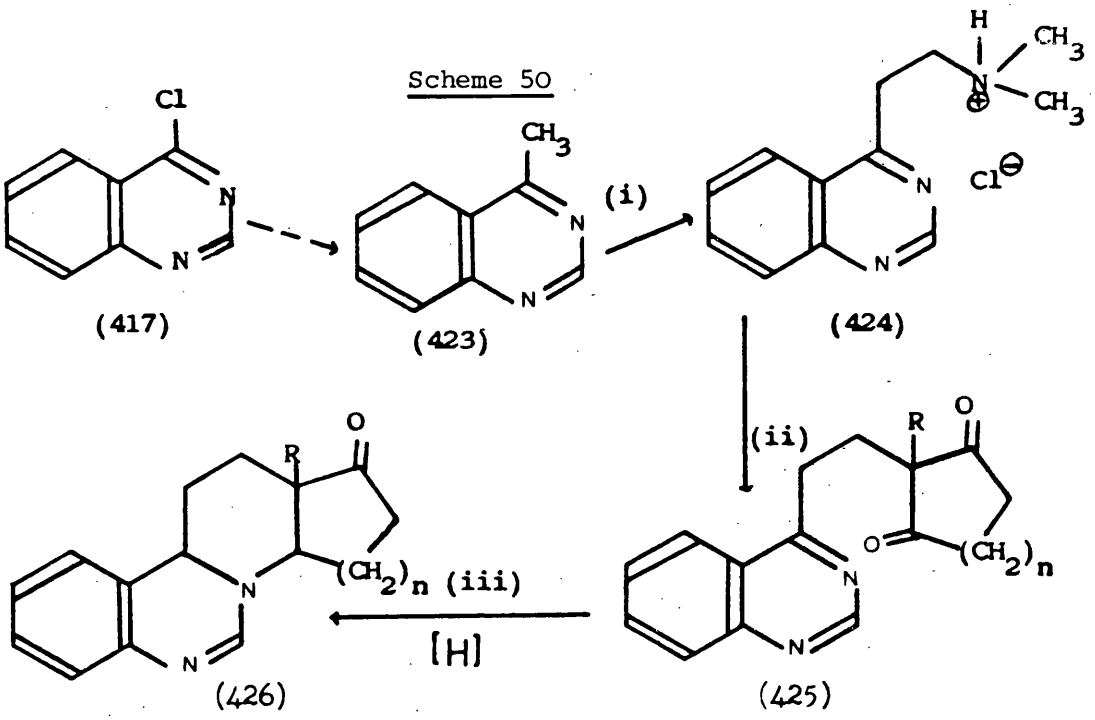
6.2 Many workers, including Jones[197] have reported diazasteroid synthesis from quinazoline derivatives. An outline of the route employed in this project leading to diazasteroids, based on the Torgov synthesis (see Section 2.3.3), is shown in Scheme 50. The main disadvantage to this route is the relative inaccessibility of the appropriate starting material (4-methylquinazoline).

Scheme 49[567]



4-Methylquinazoline was prepared *via* several methods (see Sections 6.3 and 6.4).

Scheme 50



R = CH_3, n = 1

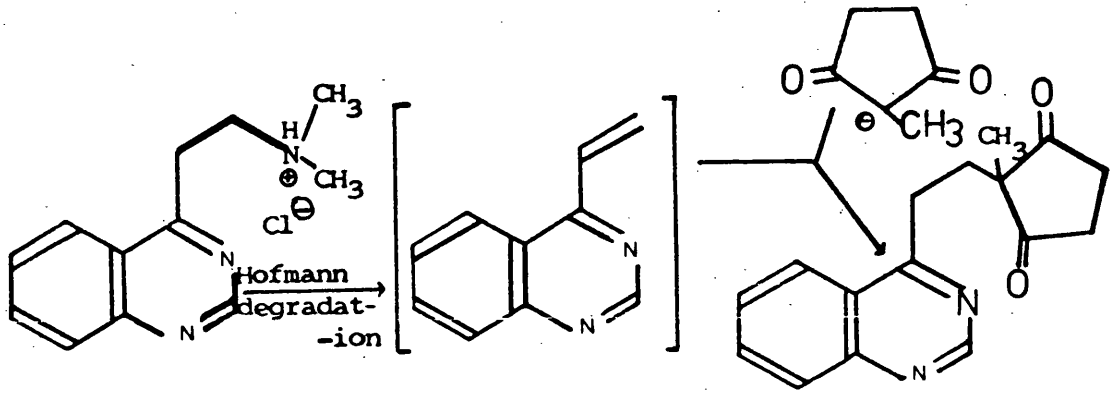
R = CH_3, n = 2

(i) Mannich reaction

(ii) Michael reaction with cyclic, 1,3-diones

(iii) Catalytic reduction

The Mannich[568] condensation of 4-methylquinazoline (423) with dimethylamine hydrochloride and formalin in ethanol afforded the Mannich base hydrochloride (424) in 91% yield, which underwent potassium t-butoxide - catalysed Michael reaction with cyclic 1,3-diones to yield intermediates (425), (see Scheme 50).

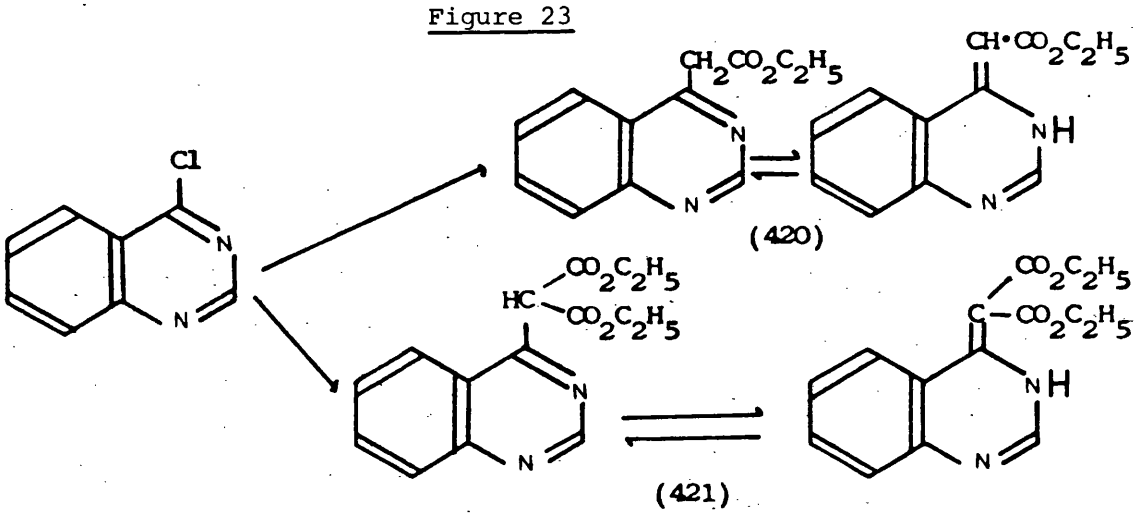


The yields at this stage were so poor (less than 10%) that catalytic reductions to furnish the required cyclized products (426), had to be abandoned.

6.3 An investigation of 4-substituted quinazolines as potential intermediates for diazasteroid synthesis

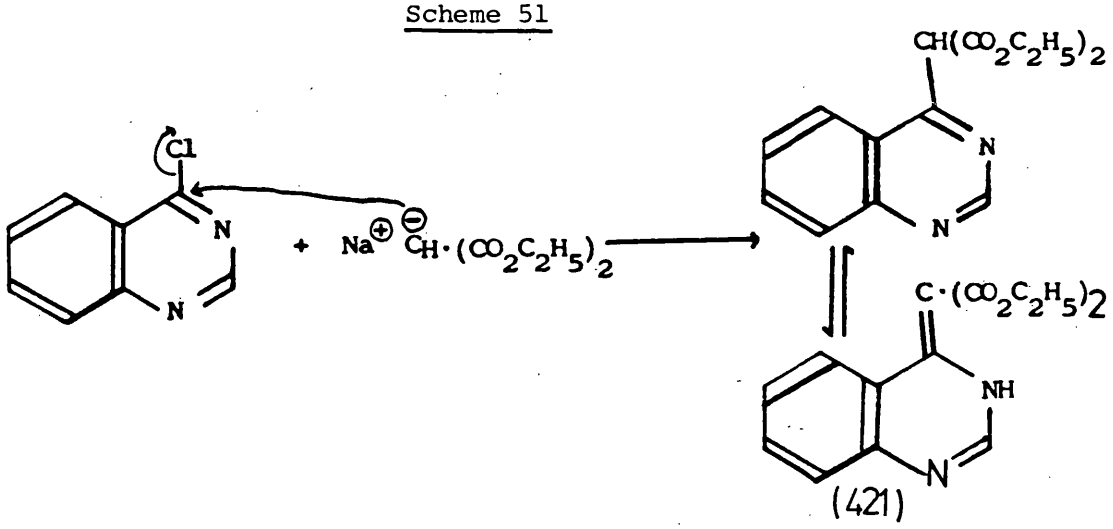
Ethyl 4-quinazolylacetate (420) was obtained by the reaction of 4-chloroquinazoline with sodio-ethylacetoacetate in yields of >55%. Similarly, diethyl 4-quinazolylmalonate (421) was obtained in 54% yield by the reaction of 4-chloroquinazoline with sodio-diethylmalonate. (see Figure 23).
Absorption peaks at $\nu_{max.}$ 3,500 cm^{-1} (>NH) and 1,710 (>C=O) cm^{-1} in the infra-red spectrum, together with the PMR - and mass - spectra (molecular ion at m/e 216) for product (420), support structure (420) as the product. (see Table 11).

Figure 23

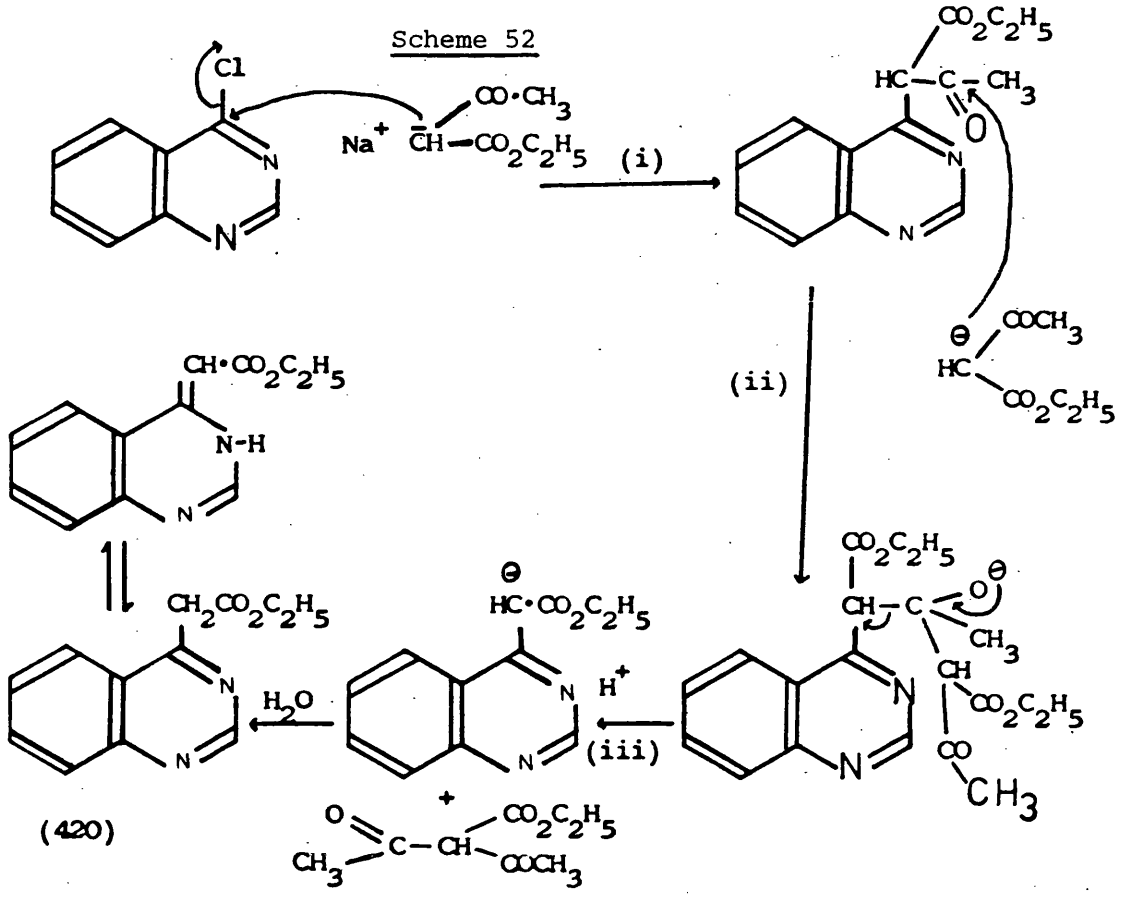


A possible mechanism for each of the above two condensation reactions is outlined in Schemes 51 and 52.

Scheme 51



Scheme 52



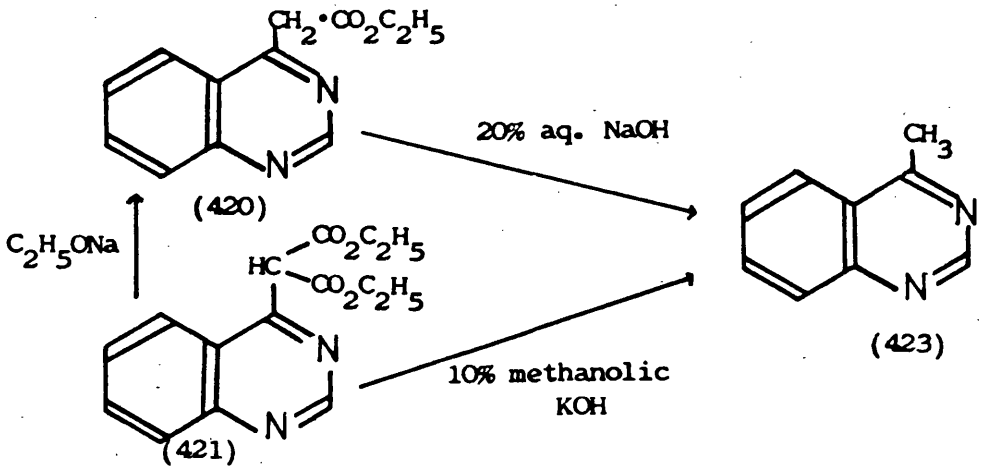
(i) Nucleophilic attack by the ethylacetoacetate anion.

(ii) Attack by a further ethylacetoacetate anion.

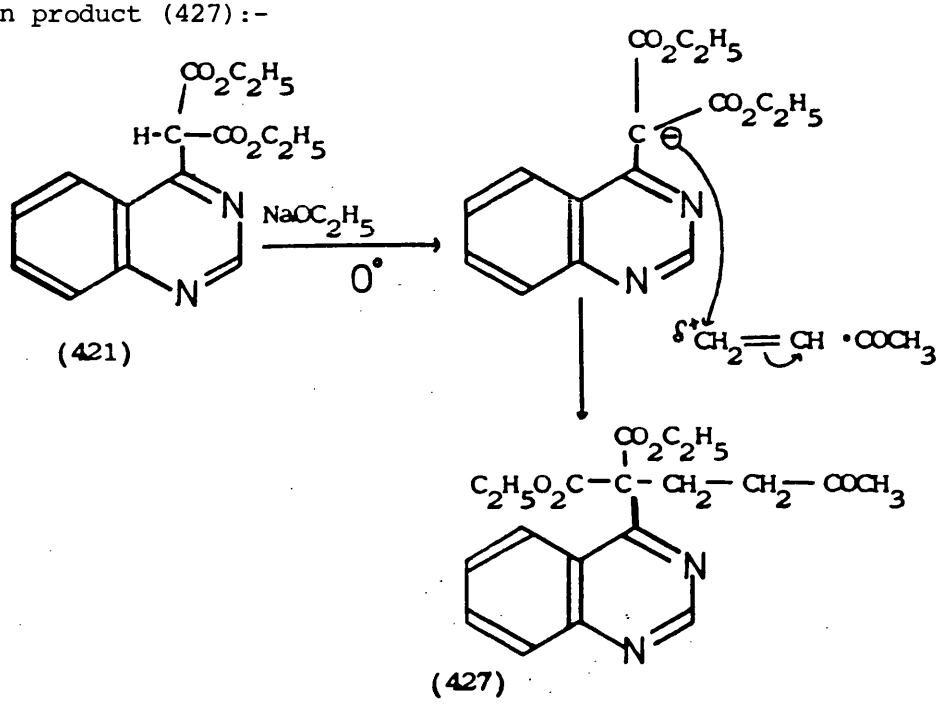
(iii) Acid-assisted cleavage of condensation product.

Alkaline hydrolysis of the monoester (420) or diester (421) furnished 4-methylquinazoline (423), with yields of 46% and

67% respectively.



The diester (421) underwent a sodium ethoxide-assisted Michael reaction with methyl vinyl ketone to give the addition product (427):-



The product (427) could not be purified satisfactorily. N-Benzoylation, N-acetylation, and N-methylation reactions were carried out on the monoester (420) and diester (421). However, proton nuclear magnetic resonance (100 MHz) and mass (low resolution) spectral evidence were not adequate to confirm the absolute structures of the products, (see Figure 24). Since there are two nitrogen atoms in the ester,

theoretically N-substitution may occur at either atom. Di-substitution did not occur. Leonard et al.[569] report several substitution reactions of 4-quinazolones at the 3-position:-

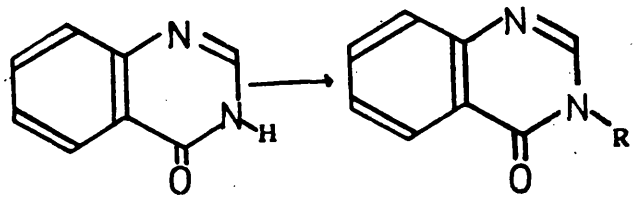
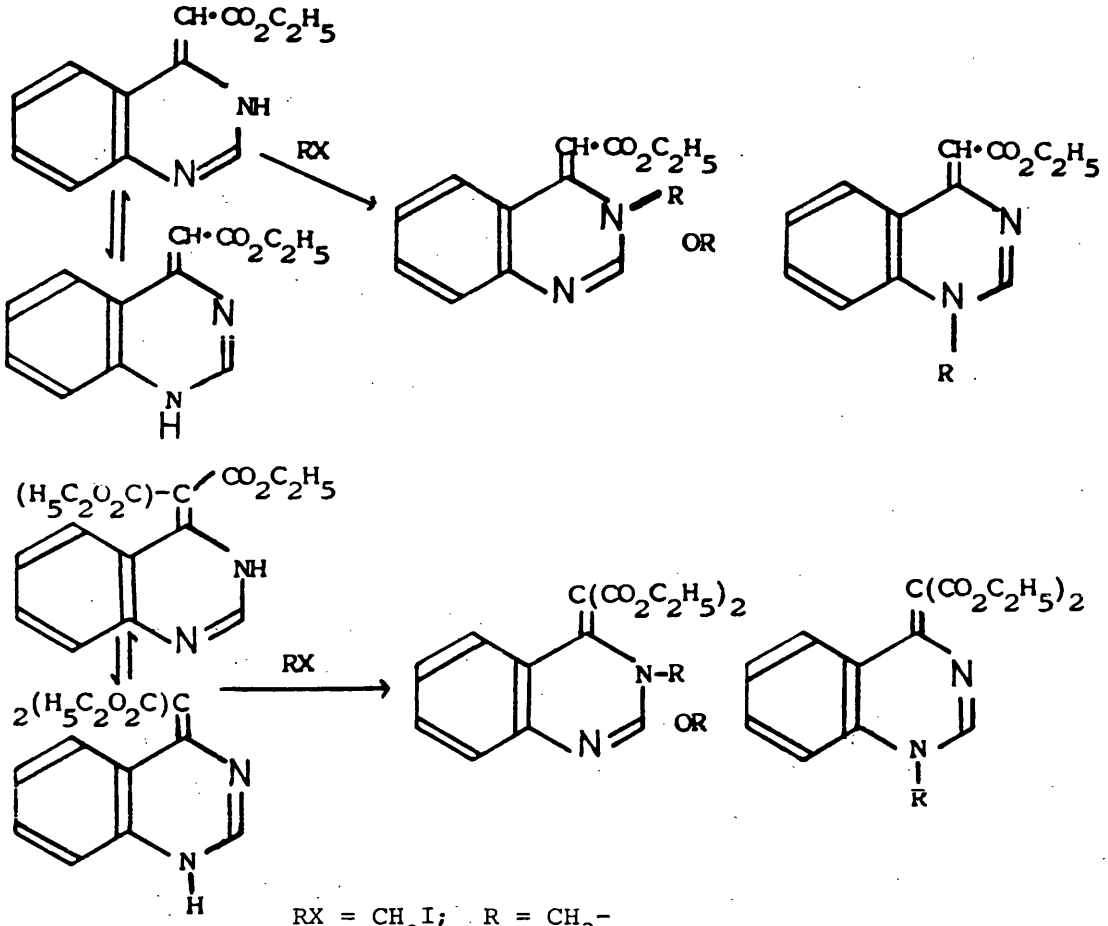


Figure 24



RX = CH_3I; R = CH_3-

RX = C_6H_5COCl; R = C_6H_5CO-

RX = CH_3COCl; R = CH_3CO-

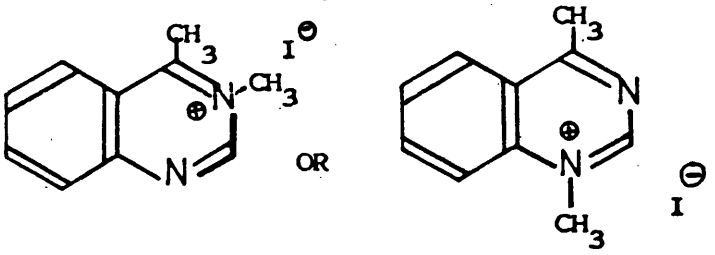


Figure 25

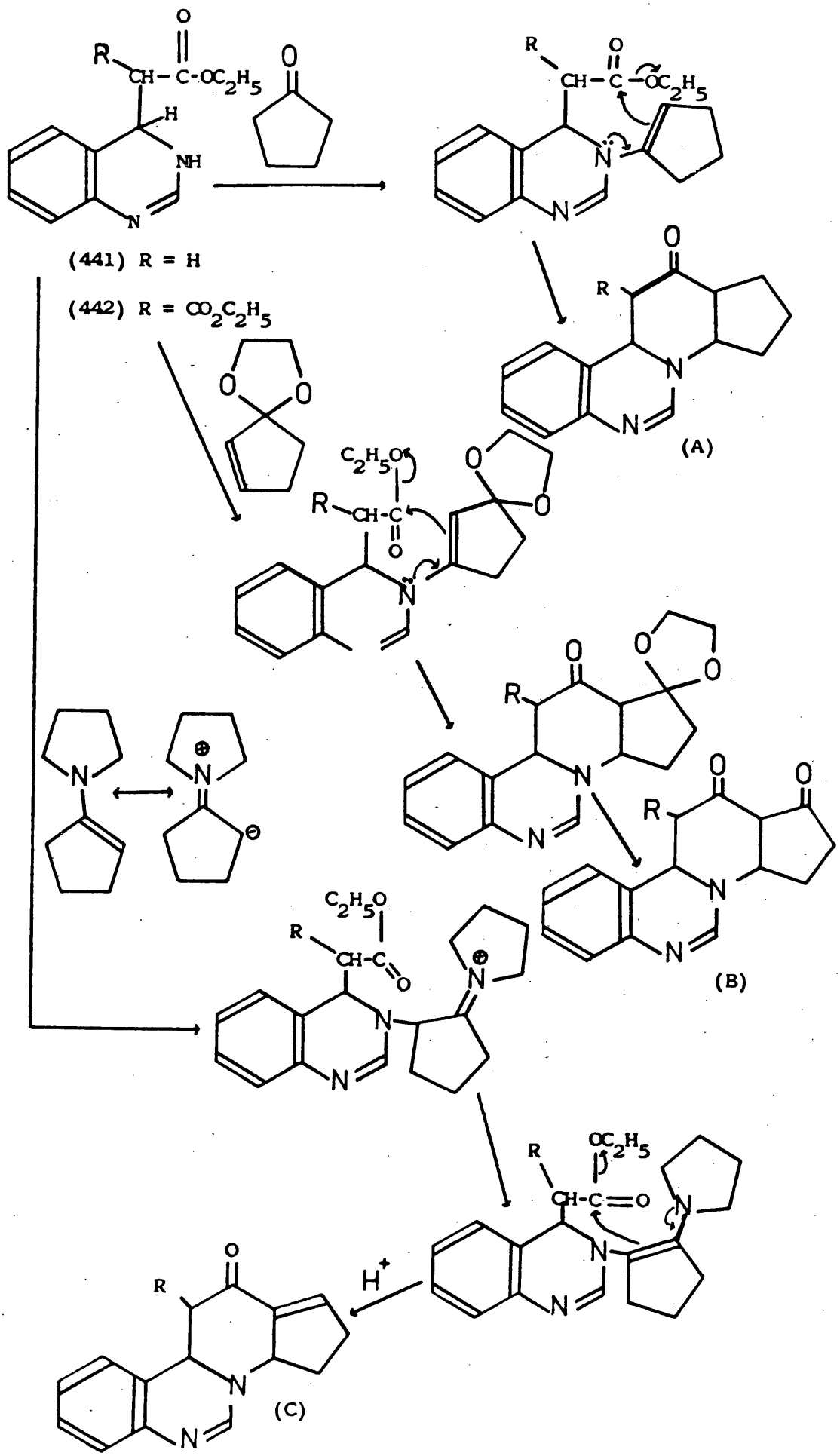


Table 11

No. of Compound (See Appendix IV for Structures)	Melting Point	Yield	$\nu_{max.}$ cm^{-1} (>C=O)	Spectra	
				PMR	Mass
				δppm from TMS (C_2-H)	m/e
(415)	215-216°	98%	1,700	8.4	146 (M^+)
(417)	97-98°	80%	-	9.2	164 (M^+)
(419)	233°	Variable	1,685	9.0	274 (M^+)
(420)	106°	54%	1,710	7.3-7.8	216 (M^+)
(421)	86°	55%	1,720	9.3	288 (M^+)
(422)	45-47°	93%	-	8.9	174 (M^+)
(423)	34-37°	67%	-	9.1	144 (M^+)
(424)	-	91%	-	9.0-9.3	200
(425)	-	-	1,710 1.685	-	268 (M^+)
(427)	-	ca.20%	-	6.8-8.1	358 (M^+)
(428)	168-170°	87%	1,660	9.0	230 (M^+)
(429)	100-105°	57%	1,700	8.1	320 (M^+)
(435)	76-79°	ca.60%	1,730 1,710 1.680	8.5	392 (M^+)

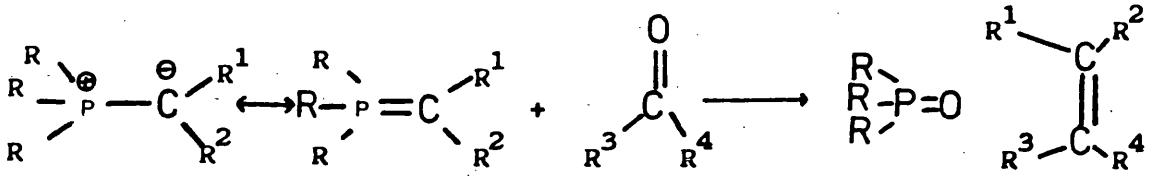
When 4-methylquinazoline was treated with a large excess of methyl iodide, the quaternary salt (436) resulted. Several attempts were made to reduce the monoester (420) and diester (421) to provide intermediates (441) and (442) respectively, which may undergo cycloaddition reactions to give the required diazasteroids, (see Figure 25). The reduced products (441) and (442), if reacted with cyclopentanone derivatives may give enamine intermediates which on cyclization, it was anticipated, might furnish diazasteroids.

Reductions of the esters (420) and (421) attempted with sodium borohydride, lithium aluminium hydride, and catalytically with platinum dioxide and palladium/charcoal up to 6 atmospheres pressure, all failed to give the required products (441) and (442). (Very high pressure hydrogenation apparatus was not available when these experiments were conducted). Later, Yamazaki et al.[570] reported the successful reduction of these esters at 120 atmospheres pressure employing Adam's catalyst. However, their attempts to react the dihydro ester (441) with cyclopentanone in presence of trifluoroacetic acid, to give the required diazasteroid (A) (see Figure 25) failed. This line of approach to the synthesis of diazasteroids was thus abandoned.

6.4 The Wittig reaction of 4-chloroquinazoline

Attempts to introduce vinylic substituents at the 4-position of the highly reactive 4-chloroquinazoline were made by employing Wittig reagents.

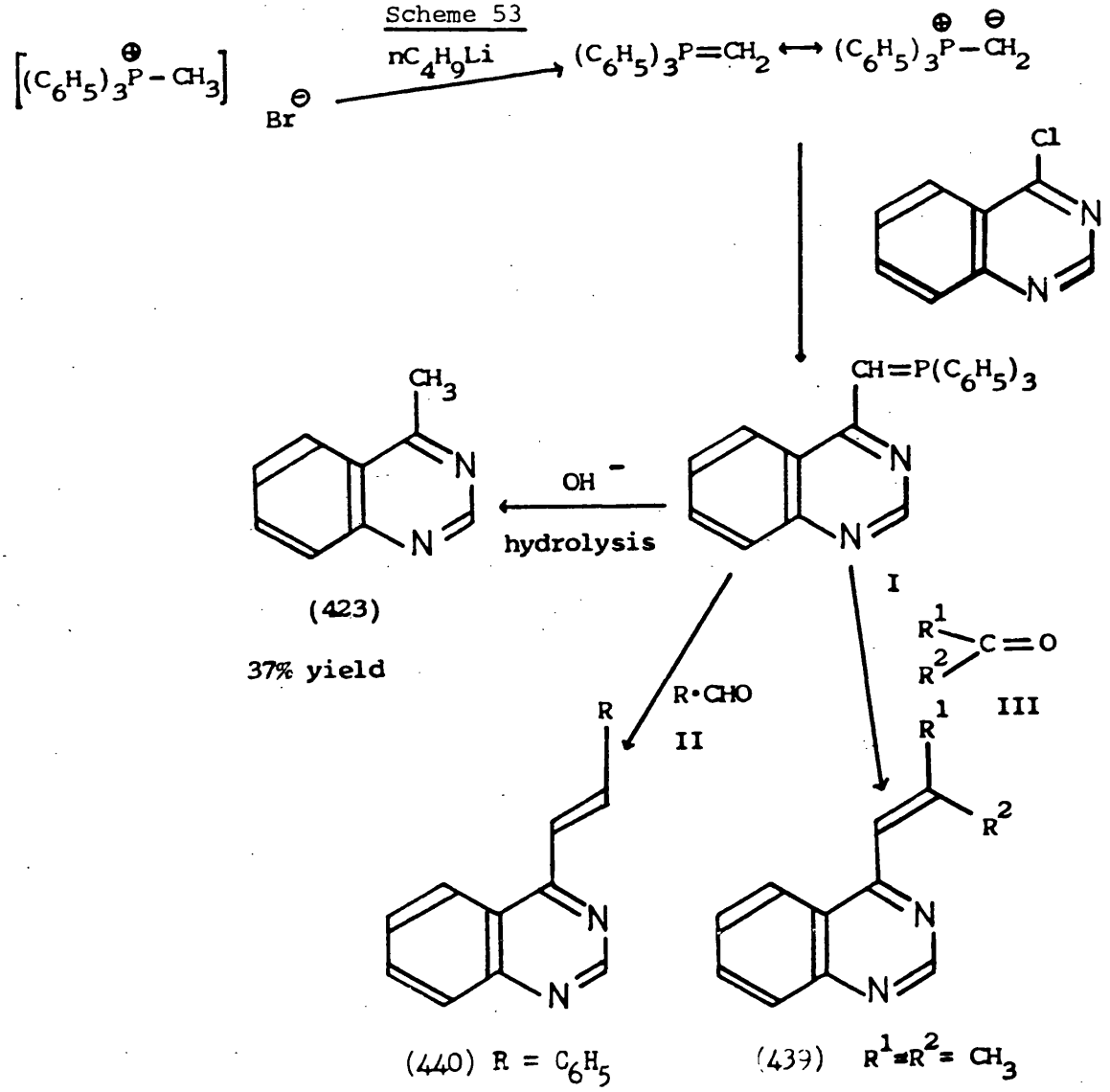
The normal Wittig reaction[577] is defined as one which occurs between the phosphonium ylid or a phosphorane, and an aldehyde or ketone, to form a phosphine oxide and an olefin:-



Ylid form **phosphorane form**

The ylid (I) generated <u>in situ</u> by the reaction of 4-chloro-quinazoline with triphenylphosphonium-methylbromide in the presence of a base (n-butyllithium), may be reacted with carbonyl compounds (II and III) or can be hydrolysed as such, to give the products shown in Scheme 53.

Scheme 53



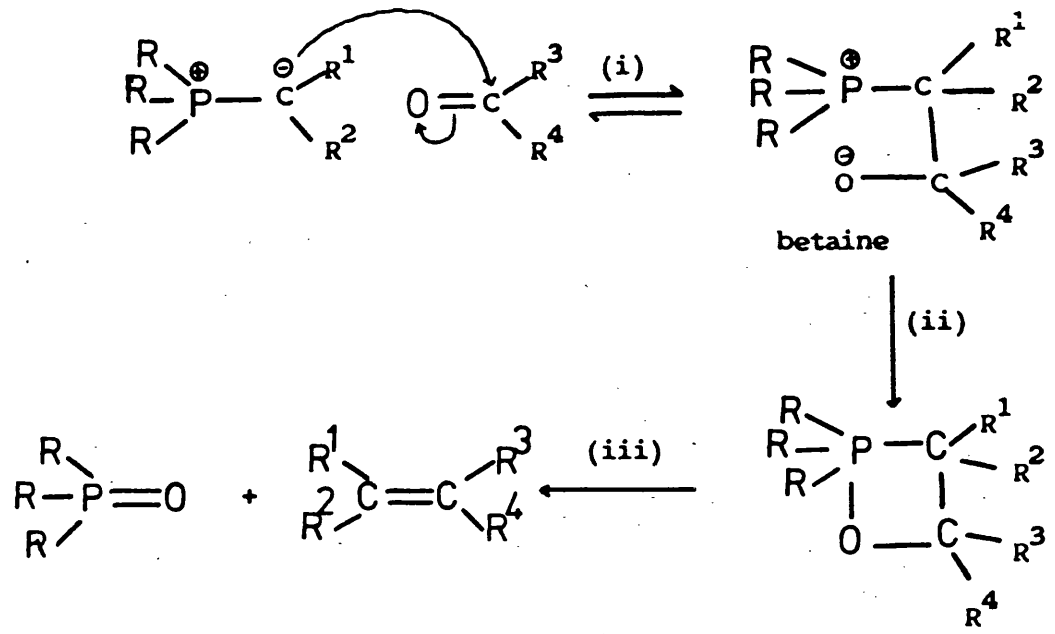
The PMR spectrum obtained for product (440) shows the C_2-aromatic proton of 4-styrylquinazoline (440) resonating at δ8.8 ppm. The remainder of the aromatic protons together with the two olefinic protons appear as a complex multiplet at δ7.3-8.4 ppm. Mass spectral evidence (molecular ion at m/e 232) also supports structure (440) for the 'diene'.

The Wittig reaction was found to be a good method for the preparation of the versatile intermediate, 4-metnylquinazoline (423). Products (439) and (440) were isolated in very low yields (< 12%), which could not be improved by modifying the reaction conditions. It may be possible to improve the yields by employing a more effective base such as potassium t-butoxide. Lithium is known for its ability to stabilize Wittig adducts, and this may be the factor hindering the progress of the reaction.

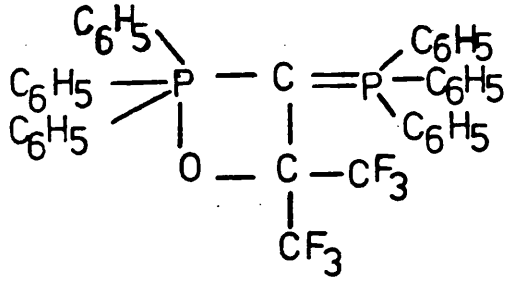
Mechanism of the reaction

Phosphoranes are resonance-stabilized structures in which there is some overlap between the carbon P-orbital and one of the phosphorus d-orbitals. Reaction with a carbonyl compound involves nucleophilic attack by the carbanionic carbon of the ylid form on the electrophilic carbon of the carbonyl group, resulting in the formation of a betaine. The betaine breaks down to the products via a four-membered cyclic 'transition state'. The driving force of the reaction is provided by the formation of the very strong phosphorus-oxygen bond. (see Scheme 54).

Scheme 54



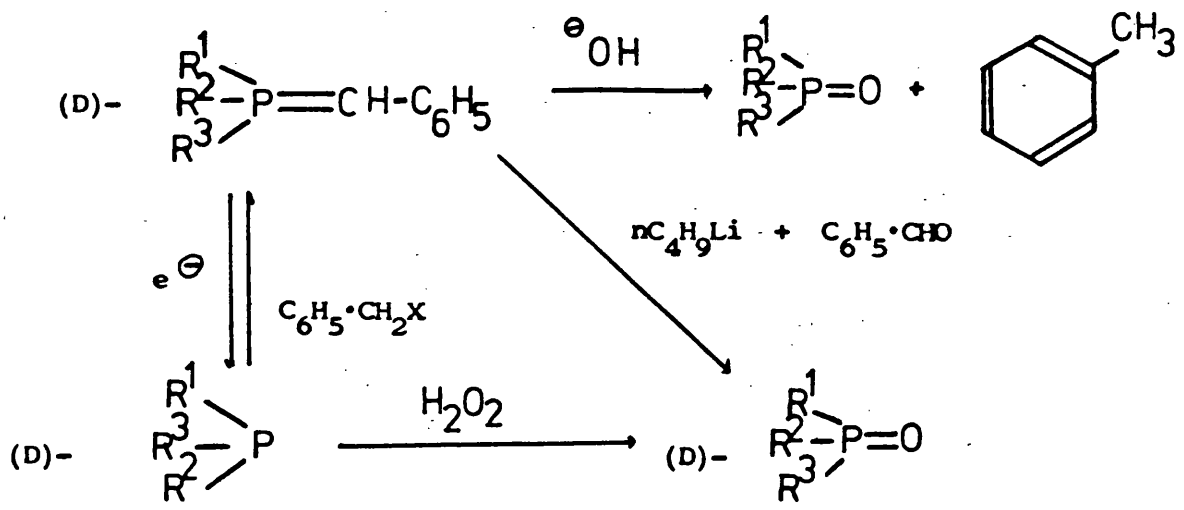
The rate-determining step is either step (i) or step (ii), depending on the nature of the reactants, and never step (iii). Although it is uncertain whether the 4-membered ring is a true intermediate or a transition state, one example of an oxyphosphorane intermediate (see below) with an axial oxygen atom as required by theory, has been isolated[571].



Experiments with optically active phosphonium salts have established that the Wittig reaction proceeds with complete retention of configuration,[572,573] as required by a cyclic mechanism (see Scheme 55).

The Wittig reaction was originally thought to be stereospecific.[574] However, it is now known that the reactions of

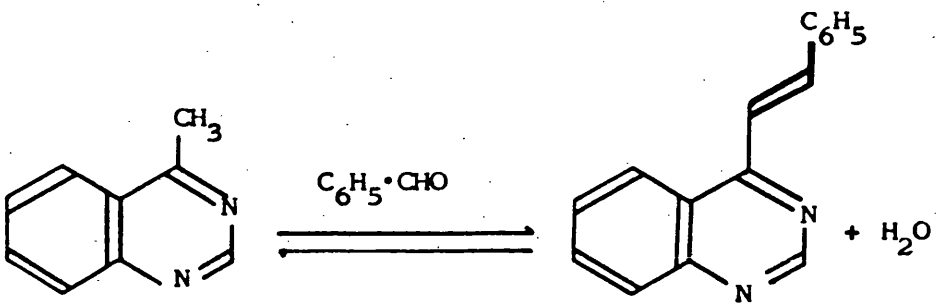
Scheme 55



unstable ylids give rise to varying ratios of cis/trans alkenes depending on the reaction conditions employed (salts present, polarity of solvents, activity of nucleophiles, etc.)[575,576]

6.5 Condensation reactions of 4-substituted quinazolines

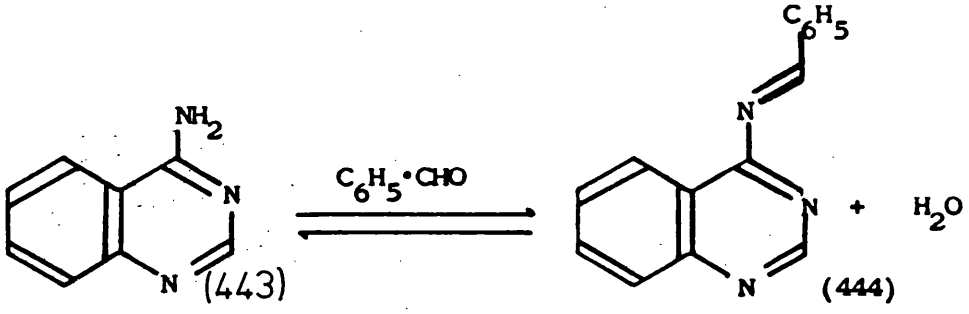
When 4-methylquinazoline was reacted with benzaldehyde in the presence of an anhydrous solvent (toluene or benzene), condensation occurred to give the "diene" (440) in 29% yield, which had also been prepared via the Wittig reaction on 4-chloroquinazoline. The reaction was carried out under Dean-Stark conditions, the removal of water during the reaction providing the driving force for the reaction. The use of a catalyst was unnecessary.



(440)

4-Methylquinazoline has one acidic proton and thus readily generates a methylene functionality which is activated by the heterocyclic ring.

Similarly, condensation of 4-aminoquinazoline[520] with benzaldehyde under anhydrous conditions, furnished the azomethine (Schiff's base) (444), in 11% yield.



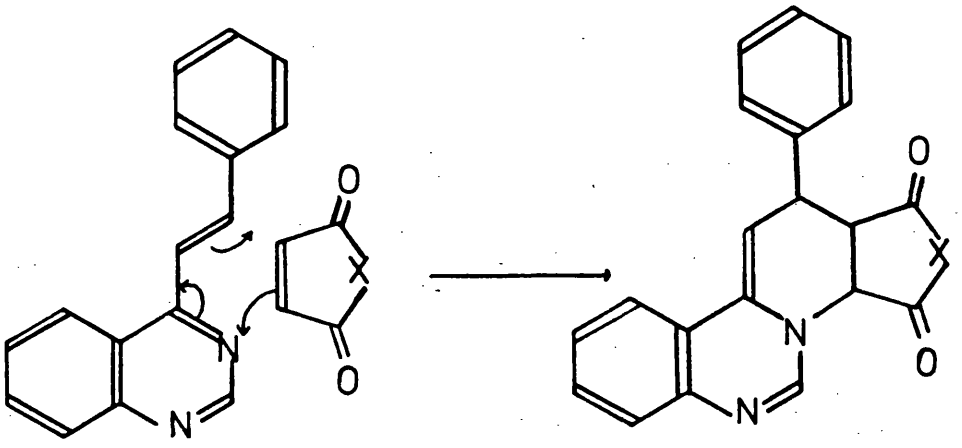
The PMR spectrum of 4-azastyrylquinazoline (444) shows the C_2-aromatic proton as a singlet at δ8.5 ppm. The remaining nine aromatic protons, together with the olefinic proton, appear as a complex multiplet at δ7.2 - 8.2 ppm. The molecular ion observed at m/e 233 by mass spectrometry, also supports structure (444).

6.6 Diels-Alder reaction of dienes (440) and (444)

The dienes (440) and (444) underwent Diels-Alder reactions with the two dienophiles (see Schemes 57 and 58) employed. For details of the mechanism of the Diels-Alder reaction see Section 5.3.3.

In this series of experiments, only two readily available dienophiles were employed. It was not possible to purify the adducts satisfactorily owing to their extremely insoluble nature. Examination of the mass spectra obtained for the crude products, indicated that adduct formation does occur.

Scheme 57



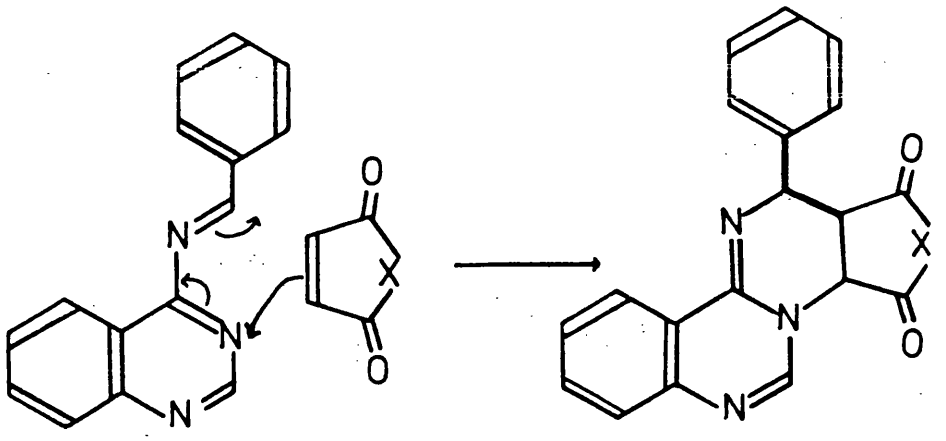
(445) X = >O

(446) X = >N·C_6H_5

The molecular ions seen on the mass spectra were in agreement with the molecular weights of the required products. However, these results are inconclusive. Further work is necessary in order to establish the nature of the products formed via these reactions.

An extension of this reaction scheme by using a wide range of dienophiles may lead to a whole series of novel di- and tri-azasteroids, some of which may have interesting pharmacological properties. Solubility was the main problem encountered with these adducts. They were found to be extremely insoluble, even in very polar solvents such as trifluoracetic acid.

Scheme 58



(447) X = $\geq O$

(448) X = $\geq N \cdot C_6H_5$

PART II RESULTS AND DISCUSSION (CONTINUED)

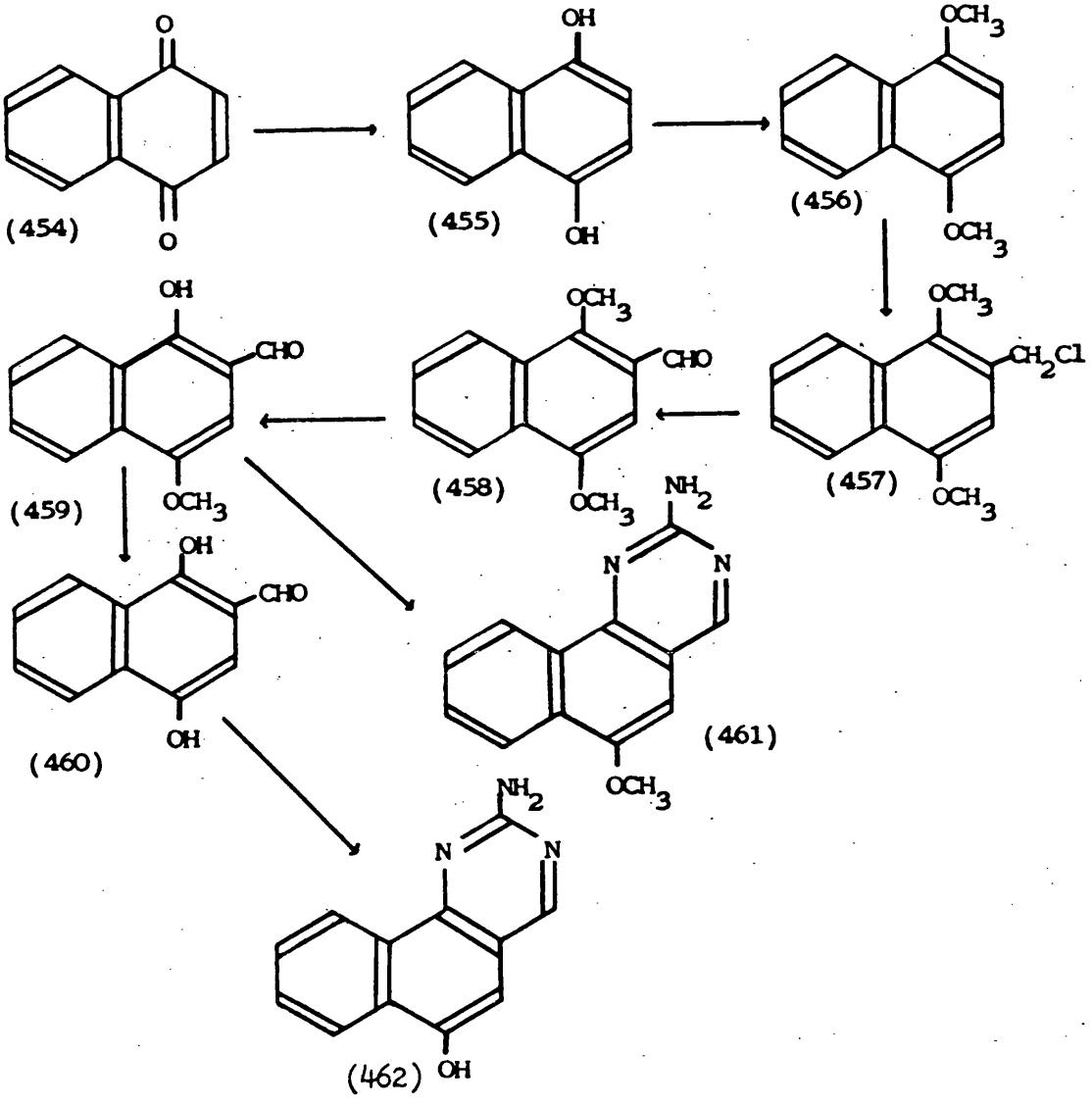
C H A P T E R S E V E N

SYNTHESIS OF TRI-AZASTEROIDS AND INTERMEDIATES FROM SUBSTITUTED NAPHTHALENES

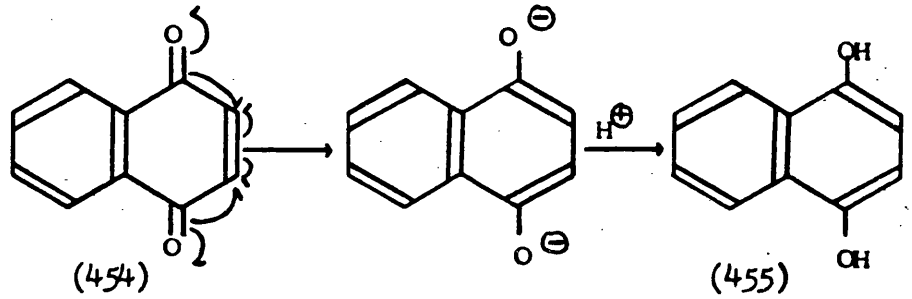
Tri- and tetra-cyclic compounds containing the guanidinium moeity were prepared by the condensation reaction of hydroxy-naphthaldehydes with guanidine carbonate.

7.1 The benzo[h]quinazoline (461) was prepared *via* the route outlined in Scheme 59.

Scheme 59

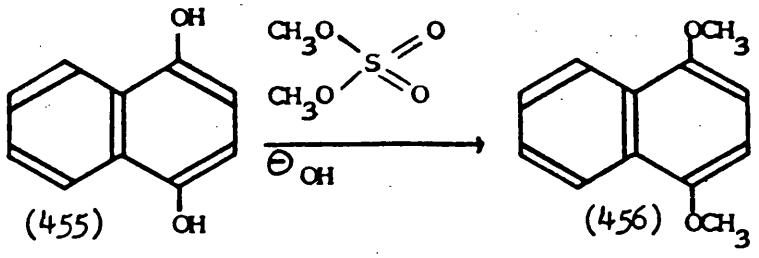


7.1.1 Reduction of 1,4-naphthaquinone (454) to 1,4-dihydroxy-naphthalene (455) with sodium hydrosulphite was a straight-forward reaction, but yields (ca. 50%) obtained were lower than expected for this type of reaction. The reduced product (455) was extremely sensitive to light and moisture, therefore suitable precautions had to be taken i.e. storage in a vacuum desiccator in the absence of light.



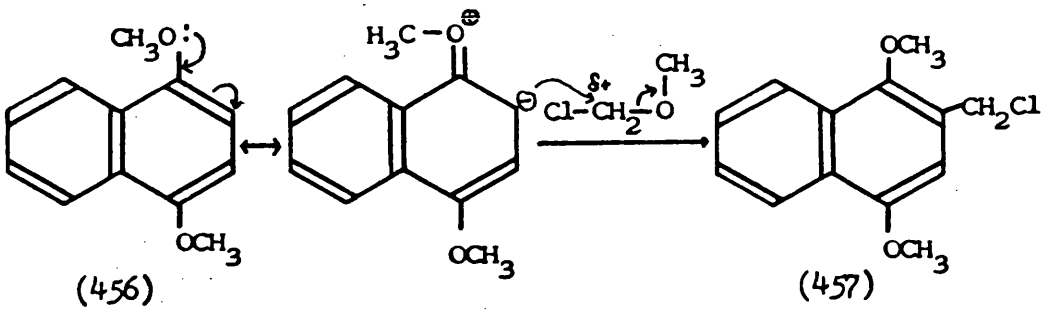
In the PMR spectrum, the two protons of the hydroxyl groups appear as a singlet at δ8.25 ppm. The six aromatic protons appear as three quartets in the aromatic region (δ6.79-8.25 ppm).

7.1.2 The methylated product (456) was obtained by the action of dimethyl sulphate in methanol on 1,4-dihydroxynaphthaline, in the presence of potassium hydroxide. Due to the instability of intermediate (455), the reaction was carried out under an atmosphere of nitrogen. The yield of product (456) was dependent on the rate of addition of potassium hydroxide solution to the reactants (the slower the addition, the greater the yield). Yields of greater than 95% could be achieved.



The PMR spectrum of product (456) shows the six protons of the two methoxy groups as a singlet at δ3.95 ppm. (See Table 12).

7.1.3 Introduction of an alkyl halide function at position 2 of 1,4-dimethoxynaphthalene (456) was brought about by the action of monochloromethyl-methylether, in glacial acetic acid solvent, on 1,4-dimethoxynaphthalene (456). Yields of up to 56% were obtained. Distillation of the crude product (457) was necessary in order to obtain pure 2-chloromethyl-1,4-dimethoxynaphthalene (457).



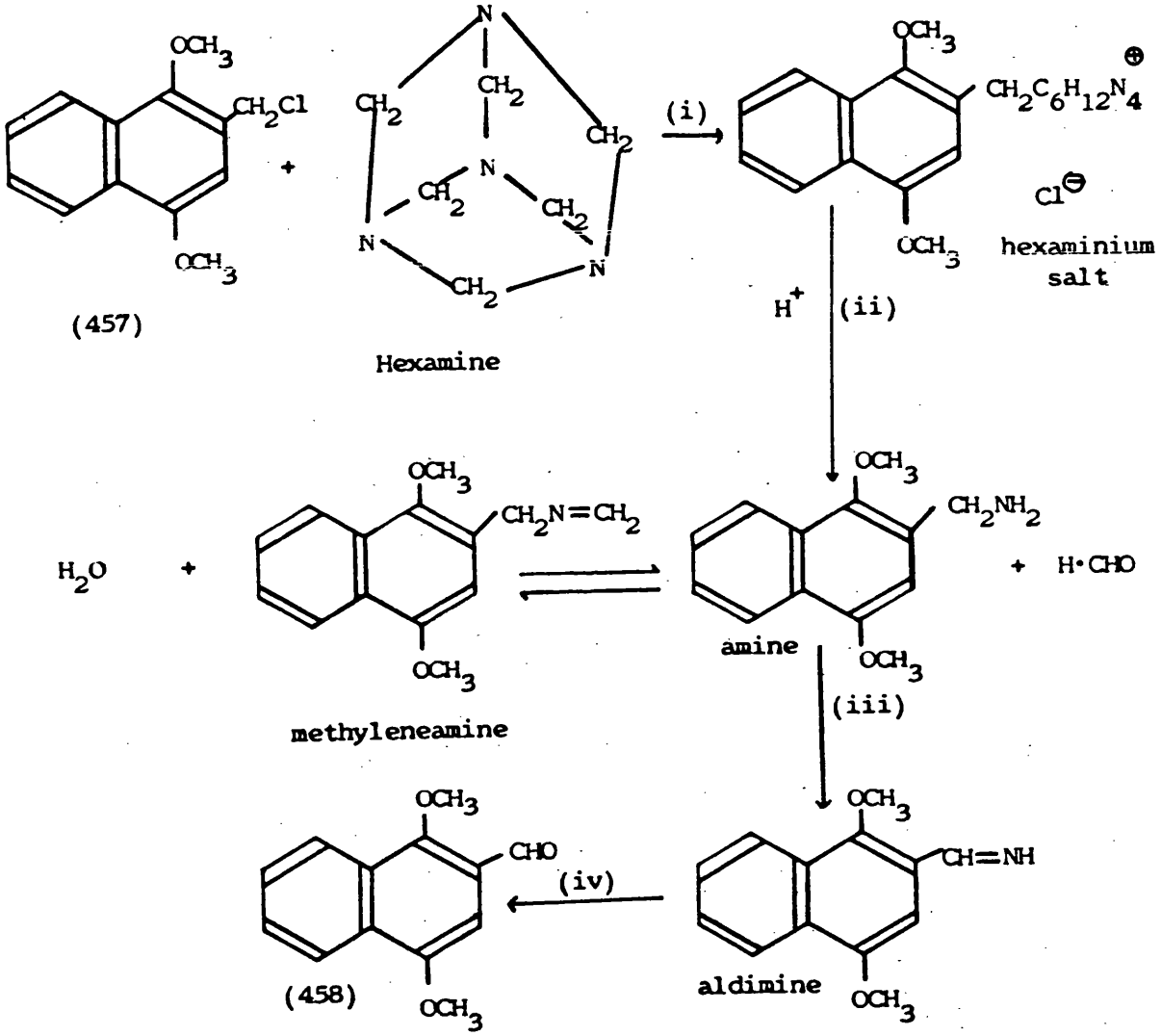
(456) (457)

The PMR spectrum obtained for product (457) shows five aromatic protons (δ6.91-8.15 ppm). The methylene chloride protons appear as a singlet at δ4.89 ppm., and the six protons of the two methoxy groups resonate as a singlet at δ3.95 ppm. (See Table 12).

7.1.4 A Sommelet reaction on the chloromethyl compound (457) furnished the aldehyde (458), in yields of up to 61%. The Sommelet reaction involves the reaction of any aryl-, aryl methyl-, or alkyl-halide with hexamine to form a hexaminium salt, which is then hydrolysed in an aqueous medium such as

aqueous ethanol or aqueous acetic acid to give the amine. The amine undergoes further hydrolysis readily to generate the aldehyde (458). A feasible mechanism for the Sommelet reaction is shown in Scheme 60.

Scheme 60



(i) Quaternary salt formation
(ii) Hydrolysis of quaternary salt to an equilibrium mixture of amine and methyleneamine.
(iii) Dehydrogenation of amine to an aldimine.
(iv) Hydrolysis of aldimine to the aldehyde (458).

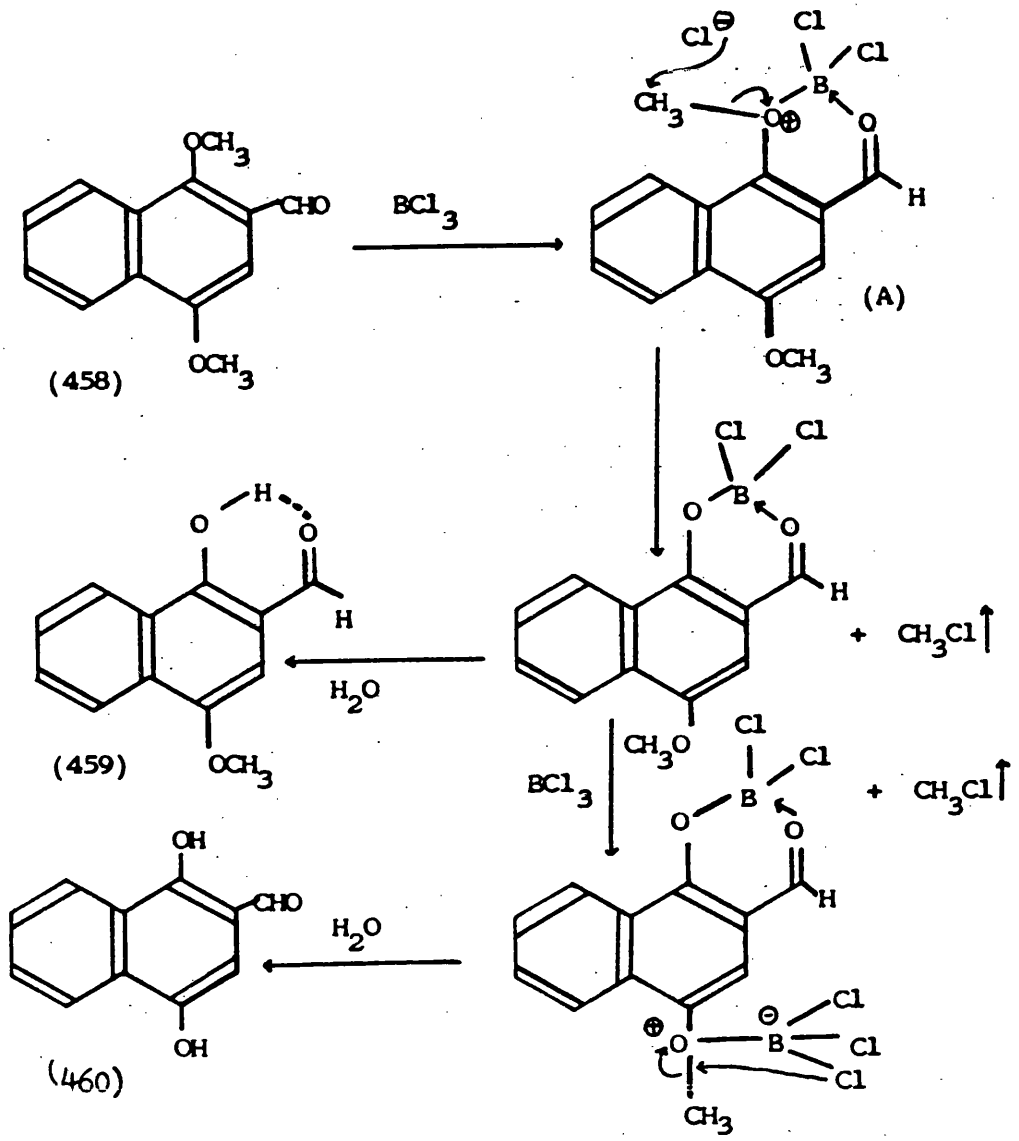
Absorption peak indicating a carbonyl group, in the infra-red spectrum of product (458), occurs at $\nu_{max.}$ 1,680 cm^{-1}. The structure for the product was further supported by PMR spectral

data. The aldehydic proton appears downfield at δ10.8 ppm. as expected, and the six protons of the two methoxy groups appear as two singlets at δ4.15 and δ4.05 ppm.

7.1.5 1,4-Dihydroxy-2-naphthaldehyde (460) was prepared by demethylation of 1,4-dimethoxy-2-naphthaldehyde with boron trichloride, in yields of greater than 90%. The reaction proceeds via the formation of a tricyclic complex (A) (see Scheme 61). 1-Hydroxy, 4-methoxy-2-naphthaldehyde(459) was prepared by selective demethylation of 1,4-dimethoxy-2-naphthaldehyde with boron trichloride (5 equivalents). The red, tricyclic intermediate (A) (see Scheme 61) was hydrolysed with water after a controlled reaction time (2 - 3h) to give the product (459). Yields of pure 1-hydroxy, 4-methoxy-2-naphthaldehyde were as high as 96%.

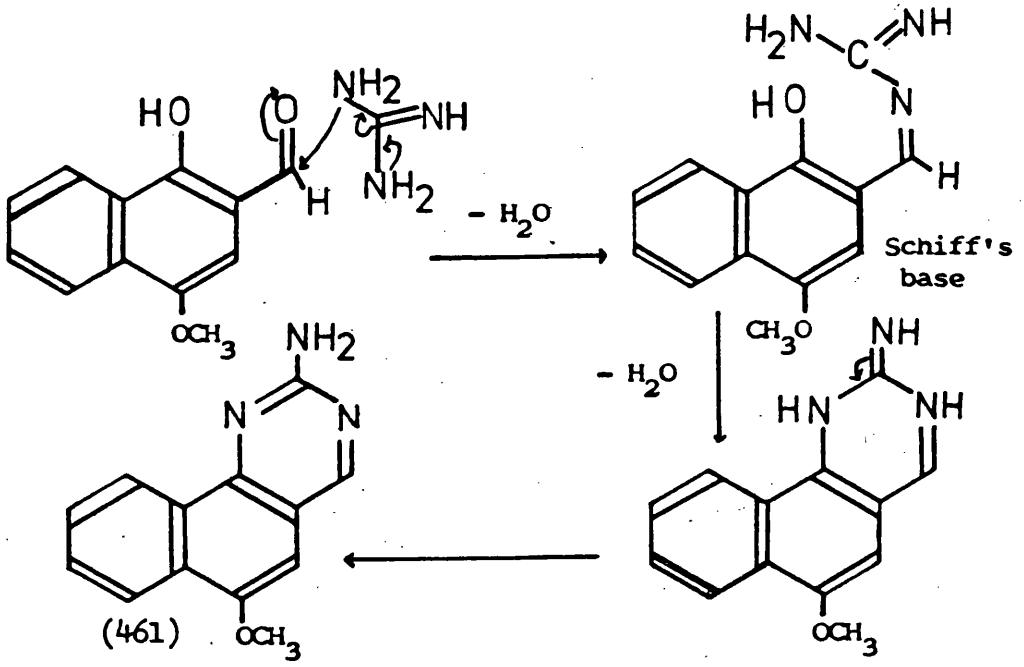
The infra-red spectrum of product (459) shows absorption peaks at $\nu_{max.}$ 3,400 cm^{-1} and 1,650 cm^{-1} due to the hydroxy and aldehyde functionalities, respectively. In the PMR spectrum, the aldehydic proton appears downfield at δ10.98 ppm. The hydroxyl proton resonates at δ9.88 ppm. The three protons of the methoxy group appear as a singlet at δ3.98 ppm.

Scheme 61[578,579]



7.1.6 The reaction of 1-hydroxy, 4-methoxy-2-naphthaldehyde with guanidine carbonate in n-octanol furnished 2-aminobenzo-[h]quinazoline (461) in low yields (ca. 19%). The condensation reaction is thought to proceed via a 'Schiff's base' intermediate (see Scheme 62).

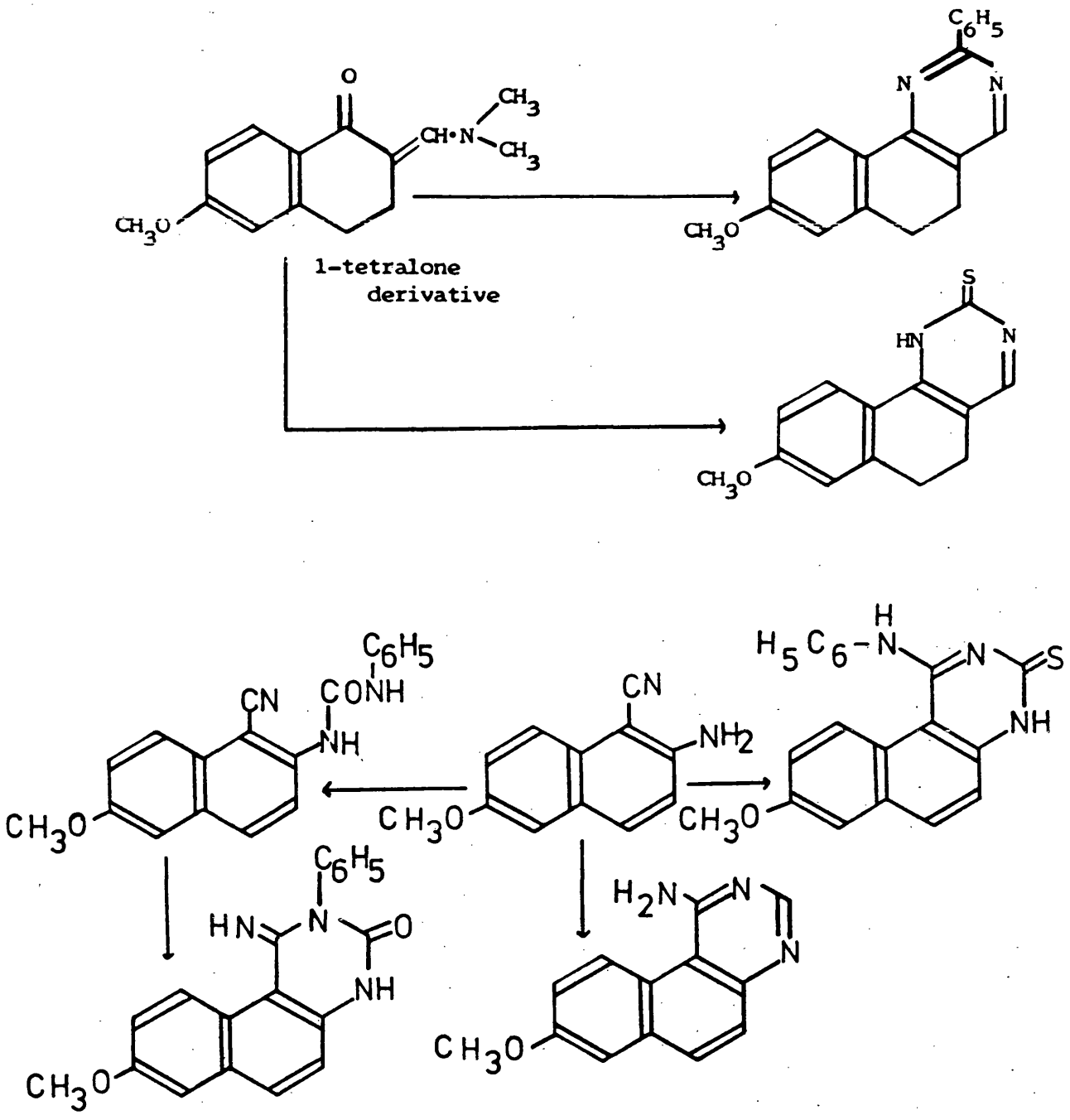
Scheme 62



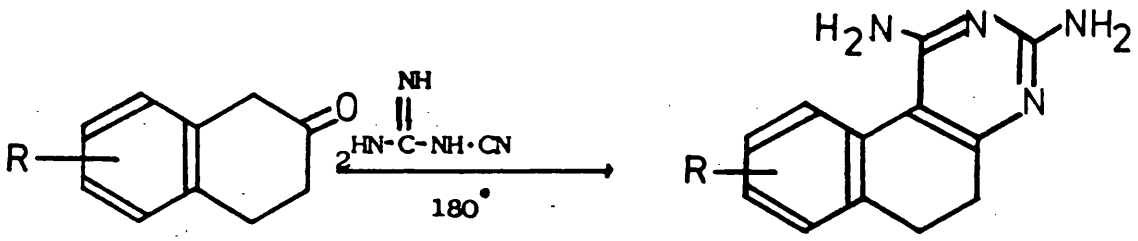
7.1.7 Other syntheses leading to benzo[f]- and benzo[h]-quinazolines

Taylor et al.[580] report the synthesis of some benzo[f]- and benzo [h]- quinazolines from o-aminonitriles, some of which are shown in Figure 26.

Figure 26

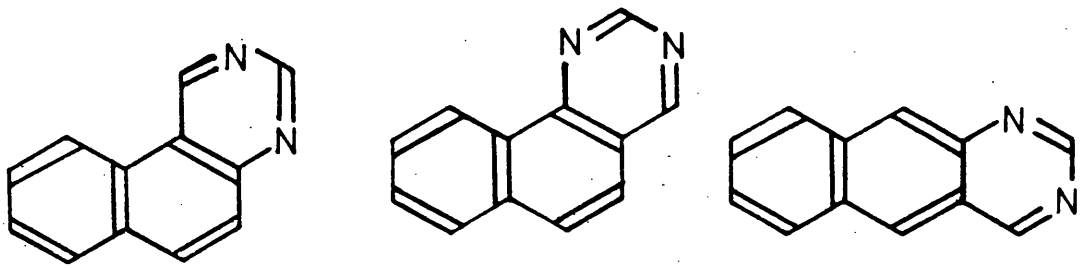


Rosowsky et al.[581,582] have prepared some benzo [f] quinazolines via the condensation of 2-tetralones with cyanoguanidine :-



Several isomeric benzoquinazolines,[583] (see Figure 27), have been prepared via the condensation of an appropriately substituted naphthyl derivative with some small nitrogen containing substrate such as guanidine, formamide, urea, etc.

Figure 27



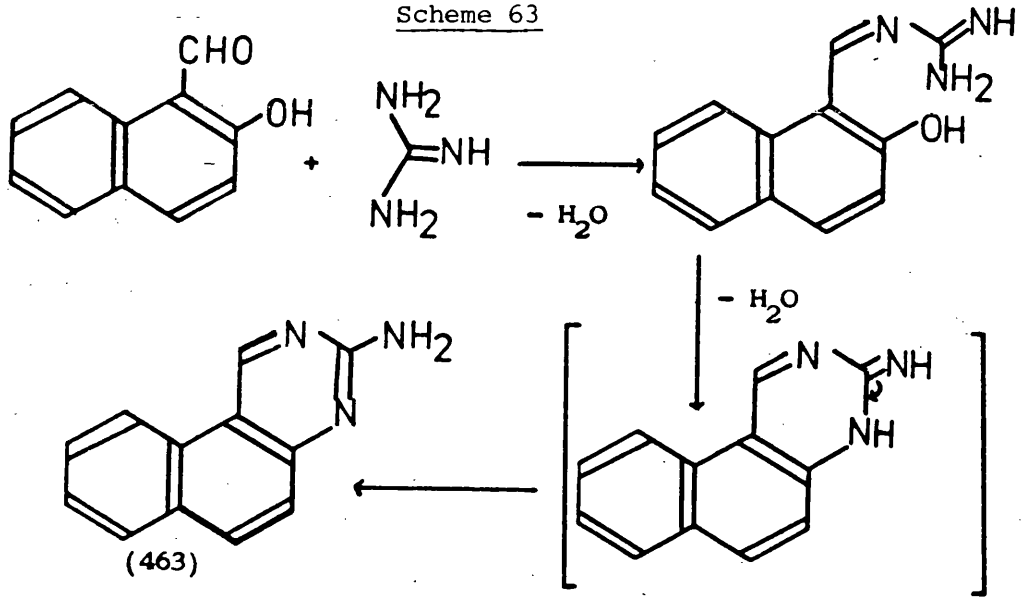
Benzo[f]quinazoline Benzo[h]quinazoline Benzo[g]quinazoline

A novel approach to the synthesis of benzo [f] quinazolines employing a preformed pyrimidine nucleus is described by Munslow and Delia.[584]

7.2 Synthesis of 3-aminobenzo [f] quinazoline

When 2-hydroxy-1-naphthaldehyde was reacted with guanidine carbonate in n-octanol, condensation occurred to furnish 3-aminobenzo [f] quinazoline in yields of ca. 25%, (see Scheme 63 overleaf).

Scheme 63

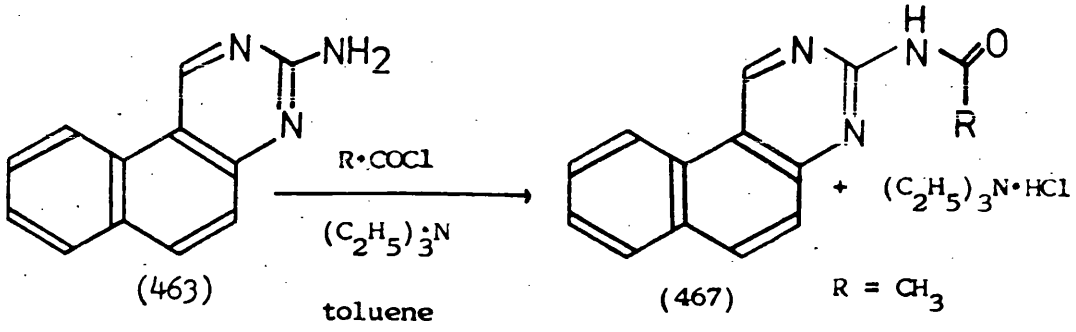


The 3-amino derivative (463) is a useful intermediate for the synthesis of triazasteroids, (see Section 7.4).

7.3 Some reactions of 3-aminobenzo [f] quinazoline

The chemistry of the amino function of this compound was investigated.

7.3.1 Reaction of the benzo [f] quinazoline (463) with acetyl chloride in the presence of triethylamine, gave the N-acetylated product (467), as expected:-



A yield of 45% was obtained for the product (467). When N-acetylation of compound (463) was attempted with acetic

anhydride as acetylating reagent, starting material (463) was recovered and no reaction occurred, suggesting that the amino function of the benzo [f] quinazoline (463) is extremely stable. This was further supported when attempts were made to replace the amino function by a hydroxy group.

7.3.2 Several attempts were made to replace the amino group of the benzo [f] quinazoline (463) with a hydroxy group, by the following reactions:-

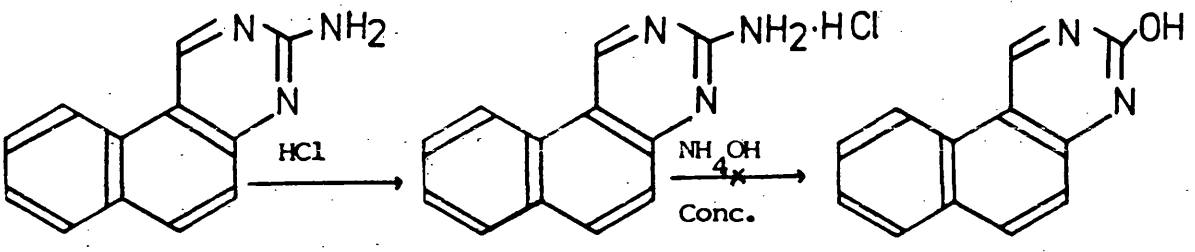
i) Reaction with hydrochloric acid

ii) Treatment with nitrous acid.

iii) Diazonium salt formation.

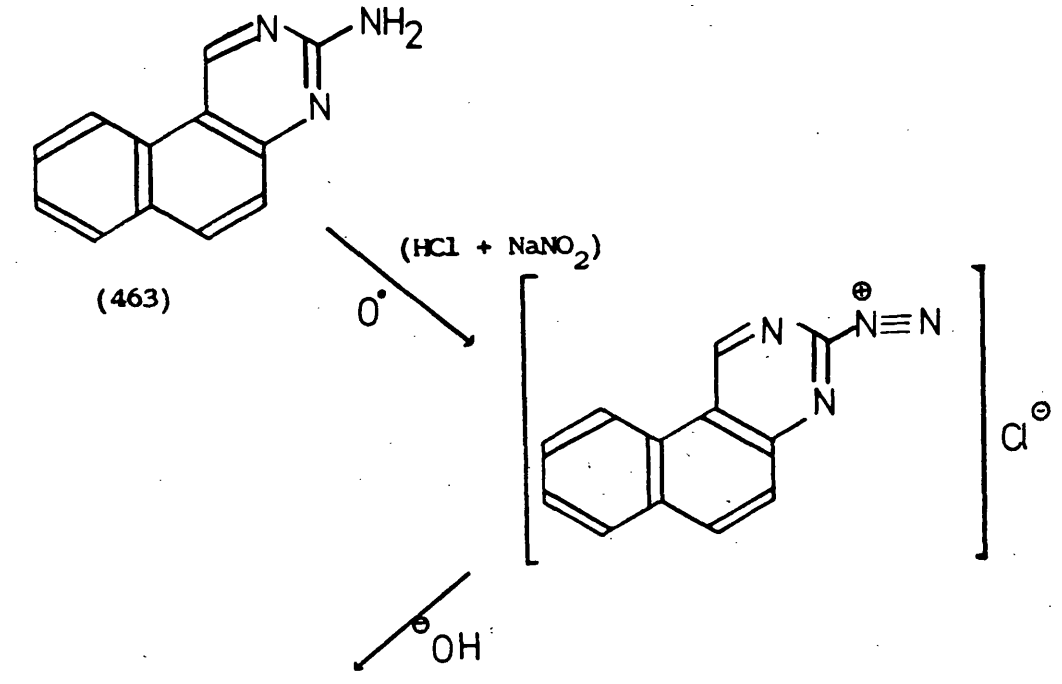
In most cases, starting material (463) was recovered on completion of the reaction.

Treatment of the benzo [f] quinazoline (463) with hydrochloric acid followed by ammonia, yielded the hydrochloride salt (465):-



(463) (465) (466)

However, the replacement was effected in high yields (ca. 75%) when the reaction was attempted via formation of a diazonium salt:-

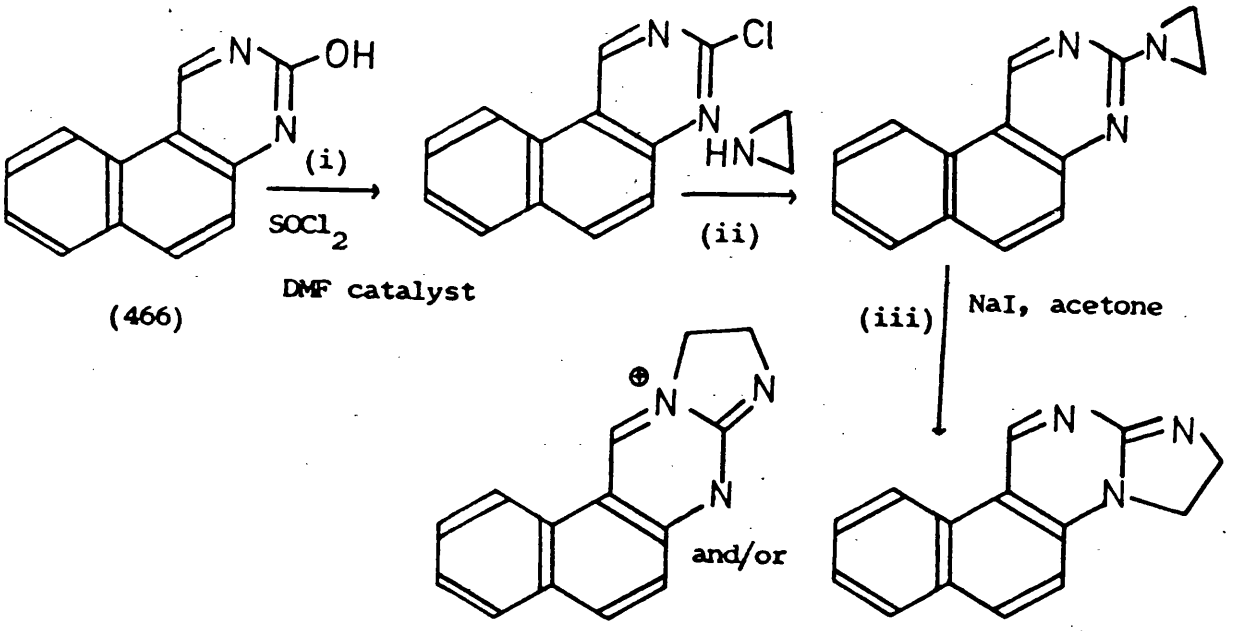


(463)

(466)

It may be possible to employ 3-hydroxybenzo [f] quinazoline as starting material for an alternative route (see Scheme 64) to the synthesis of triazasteroids (see Section 7.4).

Scheme 64



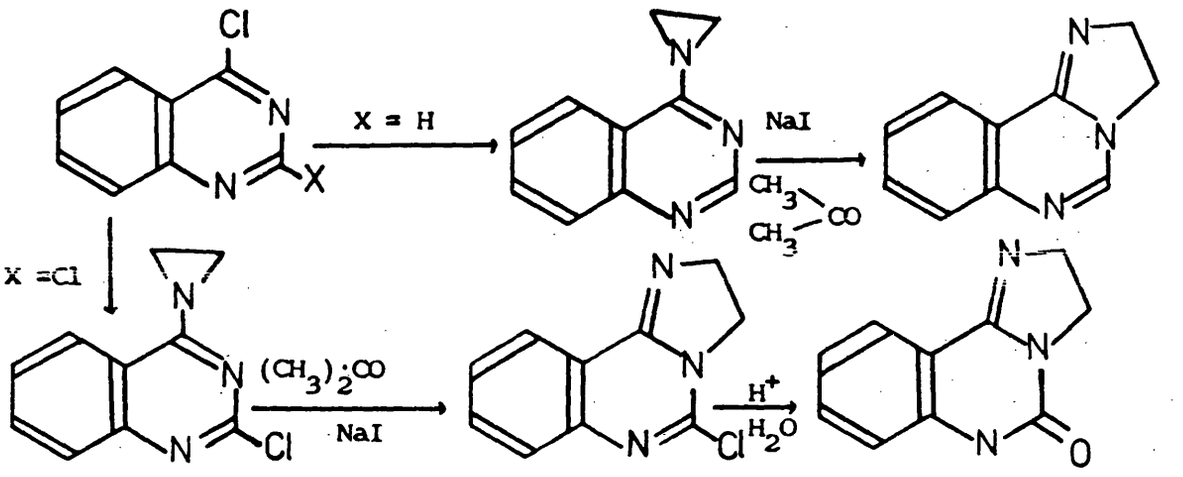
(i) Preparation of the 3-chloro derivative from the 3-hydroxy compound (466) by treatment with thionyl chloride.

(ii) Reaction of the 3-chloro intermediate with aziridine.

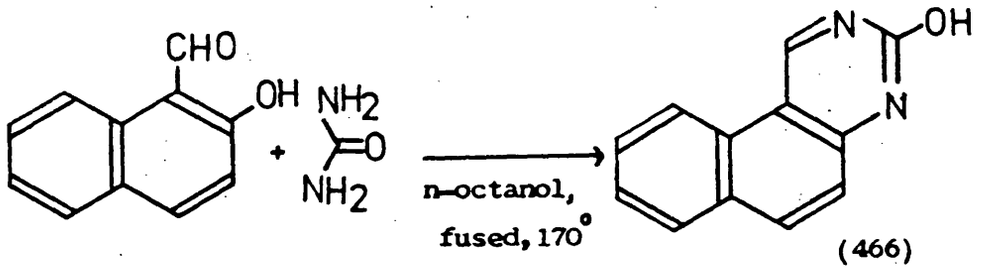
(iii) Sodium iodide/acetone-assisted rearrangement of the aziridino intermediate to give the triazasteroid shown in Scheme 64.

Stages (ii) and (iii) (Scheme 64) have been successfully attempted with 4-chloroquinazoline by Hardtmann et al.[585] and others,[586] as described in Scheme 65.

Scheme 65



3-Hydroxybenzo[f]quinazoline was also prepared via the condensation reaction of 2-hydroxy-1-naphthaldehyde with urea:-



(466)

Unfortunately, the yields obtained by this direct route were extremely poor (<10%).

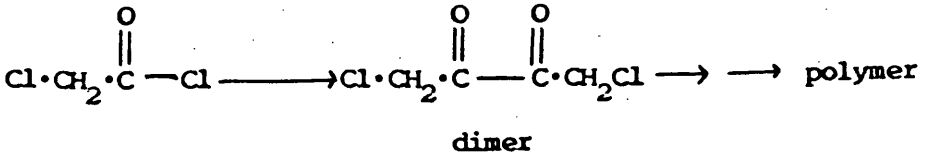
7.4 Preparation of triazasteroids via the N-chloroacetylation reaction of 3-aminobenzo[f]quinazoline

Having attempted successfully preliminary experiments to N-acetylate the 3-aminobenzo[f]quinazoline in order to establish the most favourable conditions required for the reaction, work was extended to involve N-chloroacetylation reactions of 3-aminobenzo[f]quinazoline.

Reaction conditions had to be modified several times before it was possible to isolate the required product (469). Chloroacetyl chloride was freshly distilled prior to use. Reactions were attempted in a variety of solvents, such as ethylacetate, acetone, etc. Finally, success was achieved when anhydrous toluene was employed as solvent. The reaction was carried out in the form of a suspension in toluene, under an atmosphere of nitrogen, and in the presence of a base (pyridine or triethylamine). Triethylamine was found to be too basic, reacting readily with the reagent, chloroacetyl chloride. However, pyridine proved to be an excellent base for the removal of hydrogen chloride generated during the reaction, by salt formation.

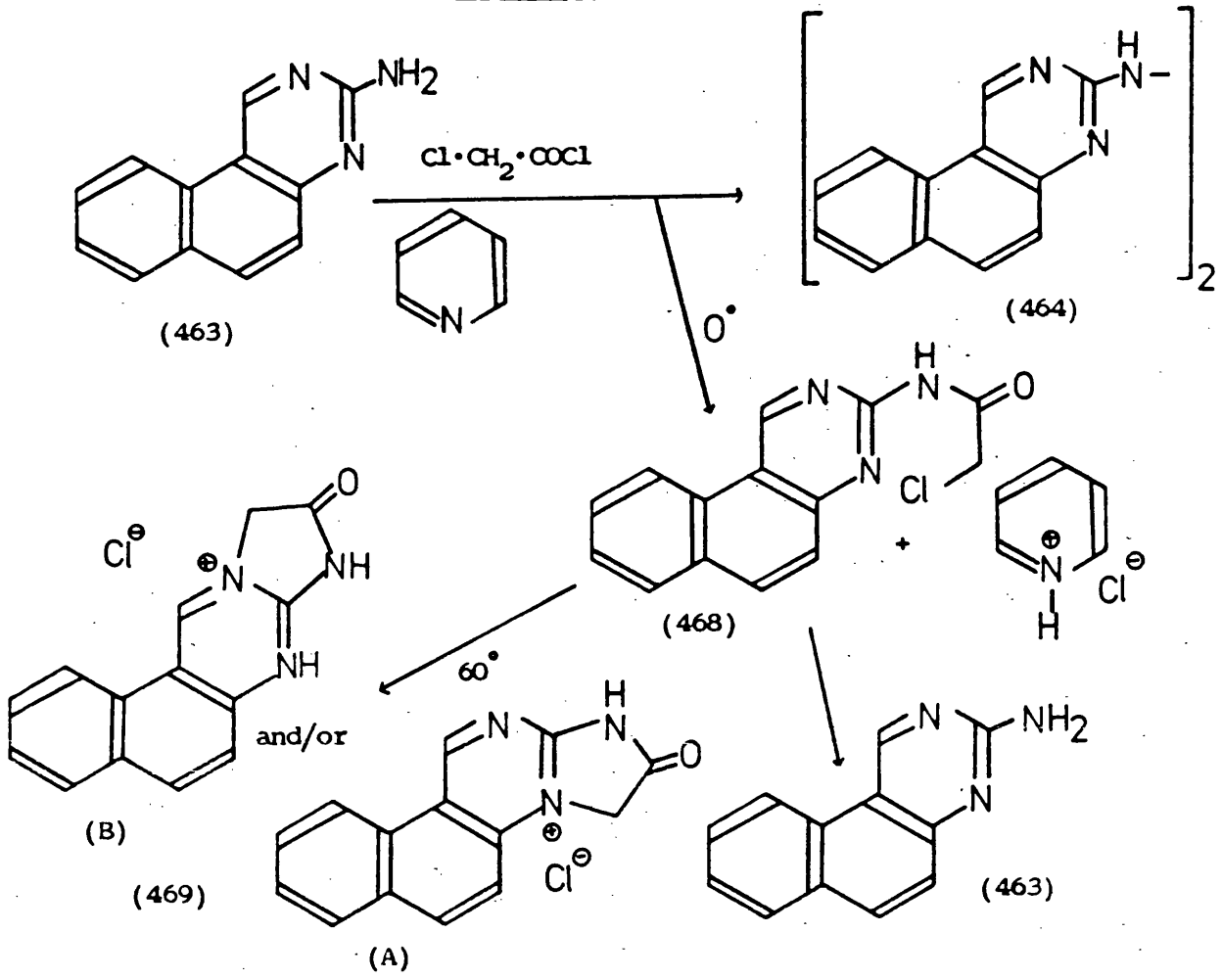
When reaction conditions employed were too vigorous i.e. too high a temperature or large excess of reagent (chloroacetyl chloride), the dimer (464) was the major isolable product, contaminated with some starting material (463).

The reagent (chloroacetyl chloride) had to be added very slowly, at 0^{o}, with a microlitre syringe to prevent self-polymerisation:-



The initial stage of the reaction was carried out at 0°, then the temperature raised gradually to ca. 60° in order to effect cyclization of intermediate (468). See Scheme 66. Although the product (469) was isolated as 43% yield of pure compound, it is not certain which isomeric form (A or B) is present.

Scheme 66



Data obtained by elemental analysis and mass spectrometry confirm the structure to be either one or both of the two forms (469) (Scheme 66). Satisfactory proton and carbon-13 nuclear magnetic resonance data was not obtainable owing to

the extremely insoluble nature of product (469). Further experimental and spectroscopic data is required in order to establish an absolute structure for product (469).

Table 12

No. of Compound (see Appendix IV for structures of compounds)	Melting Point	Yield	Mass Spectral Data (m/e)
(455)	175-176°	50%	160 (M^+)
(456)	86-87°	95%	188 (M^+)
(457)	63-64°	56%	237 (M^+)
(458)	117°	61%	216 (M^+)
(459)	85-86°	96%	202 (M^+)
(460)	190-192°	97%	188 (M^+)
(461)	293-296°	19%	225 (M^+)
(463)	257-259°	25%	195 (M^+)
(466)	328-331°	75%	196 (M^+)
(467)	210-214°	45%	237 (M^+)
(468)	-	-	271 (M^+)
(469)	283-285°	43%	236 (M^+)

PART II RESULTS AND DISCUSSION (CONTINUED)

CHAPTER EIGHT

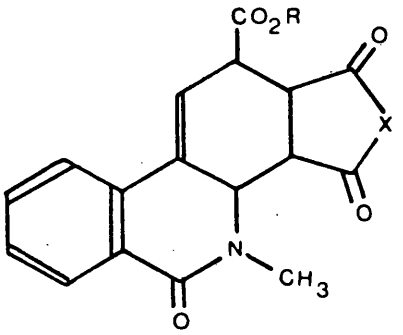
BIOLOGICAL RESULTS AND FUTURE STUDIES

8.1 Pharmacological Activity

A few compounds (see Figure 29) were tested for anti-convulsant activity by Organon Laboratories. An outline of the experimental procedures is given in Appendix III.

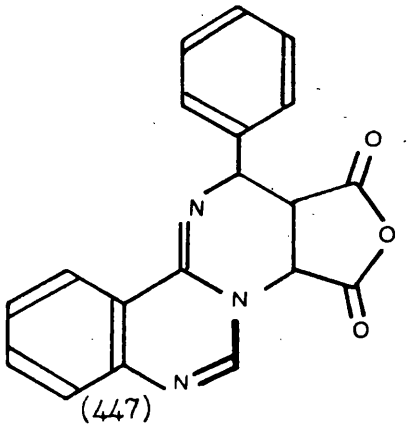
The samples which were tested, showed no significant anticonvulsant or inotropic activity.

Figure 29

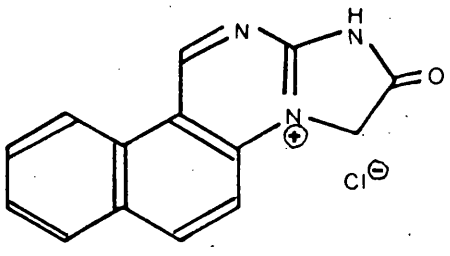


R	X
CH_3	$>N-C_6H_5$
CH_3	$>O$
CH_3	$>CH_2$
C_2H_5	$>O$

Further CNS screening of these compounds and the compounds derived *via* the quinazoline route, especially (447) and (469), is necessary before a conclusion can be drawn as to the pharmacological activity of these nitrogen-containing 'steroidal' products.



(447)



(469)

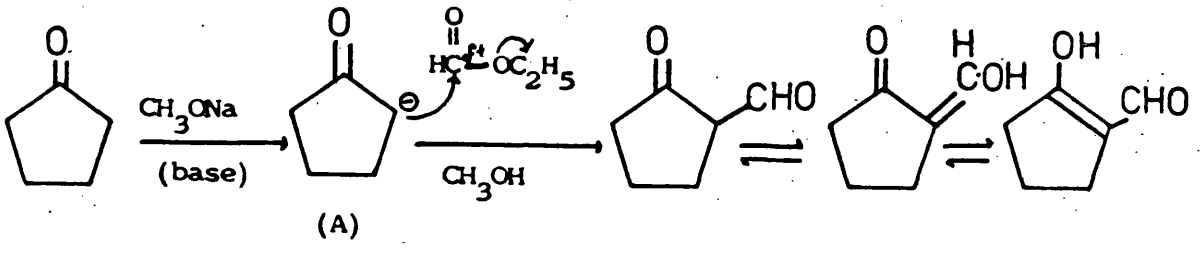
Biological evaluations of the quinazoline-based structures were not made during the course of this work, as sufficient quantities (ca. 1.0 g) of analytically pure products were not available.

8.2 Suggestions for further work, including some extensions of the routes already employed (Chapters 5, 6 and 7), leading to the synthesis of azasteroids

Several modifications and extensions to the routes employed, together with many alternative routes, were considered. Some of which, described below, may be of interest at a later date.

8.2.1 Diazasteroid synthesis from substituted quinazolines

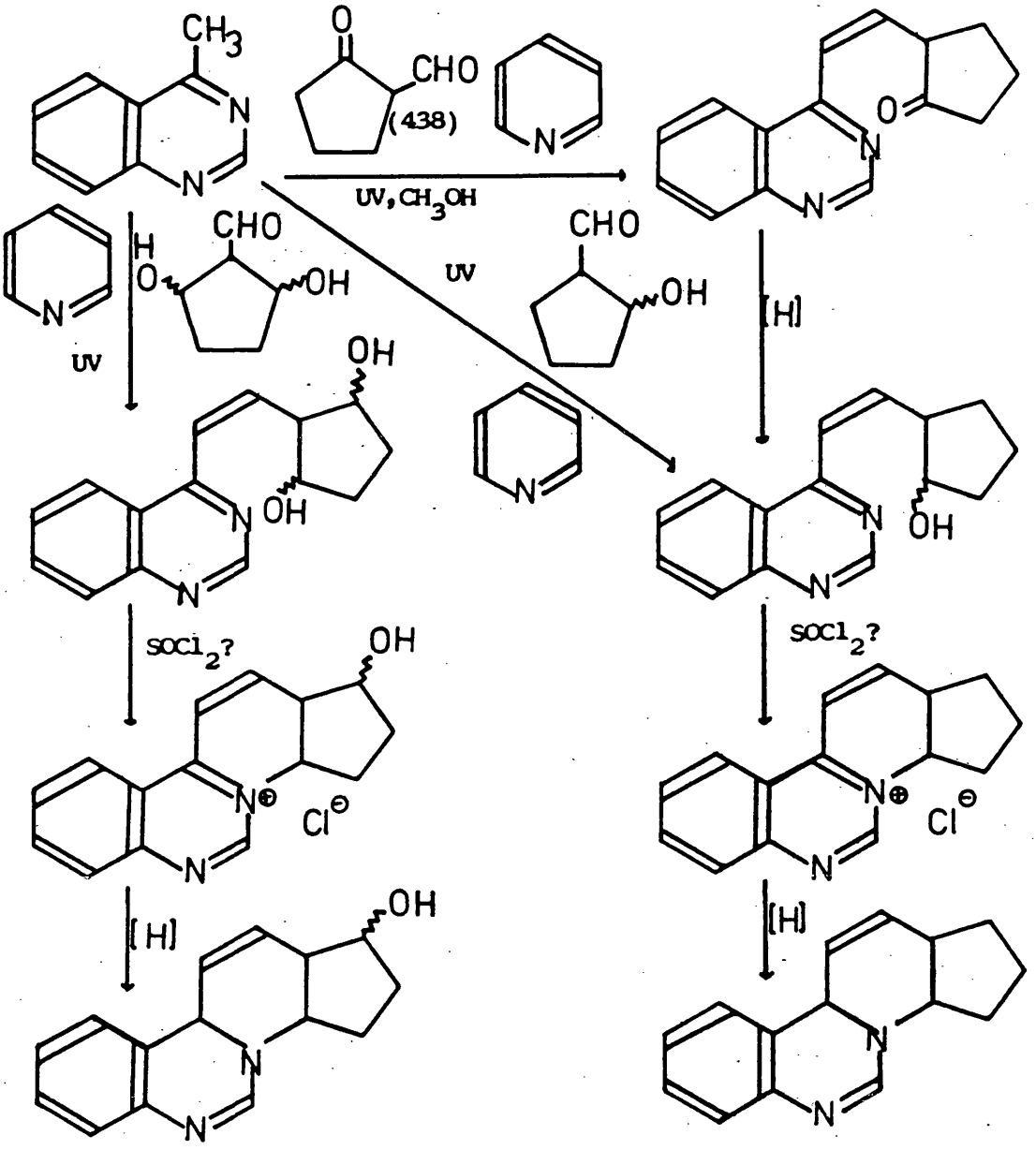
8.2.1.1 4-Methylquinazoline, if reacted with suitable cyclopentanone and cyclohexanone derivatives, may give the required diazasteroids. Condensation of 4-methylquinazoline with cyclopentanone-2-aldehyde or cyclopenta-1,3-diol-2-aldehyde, may yield the diazasteroids shown in Scheme 67. Ultra-violet light - assisted condensations may occur selectively to give the cis isomer only (with no formation of the trans). The starting material (438) prepared in low yields (ca. 16%) was found to be extremely unstable:-



(A)

The yields for this reaction are poor since the anion (A) can undergo self-condensation.

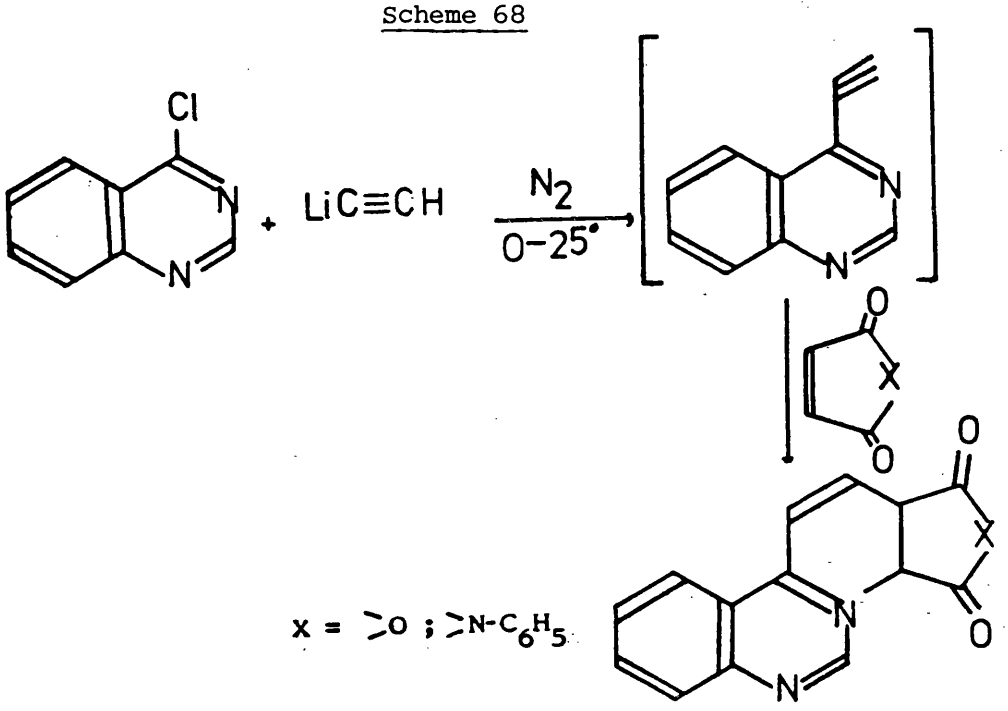
Scheme 67



8.2.1.2 Reaction of lithium or sodium acetylide with 4-chloro-quinazoline may yield intermediates suitable for the synthesis of diazasteroids.

Lithium acetylide-ethylenediamine complex ($HC \equiv CLi.H_2N.CH_2.CH_2.NH_2$) was reacted with 4-chloroquinazoline in anhydrous, freshly distilled dimethylsulphoxide, (see Scheme 68). To the resulting 4-acetylenoquinazoline a dienophile was added and the mixture stirred for a further 24h., under an atmosphere of nitrogen at 25°. Although the reaction was attempted several times, employing

Scheme 68

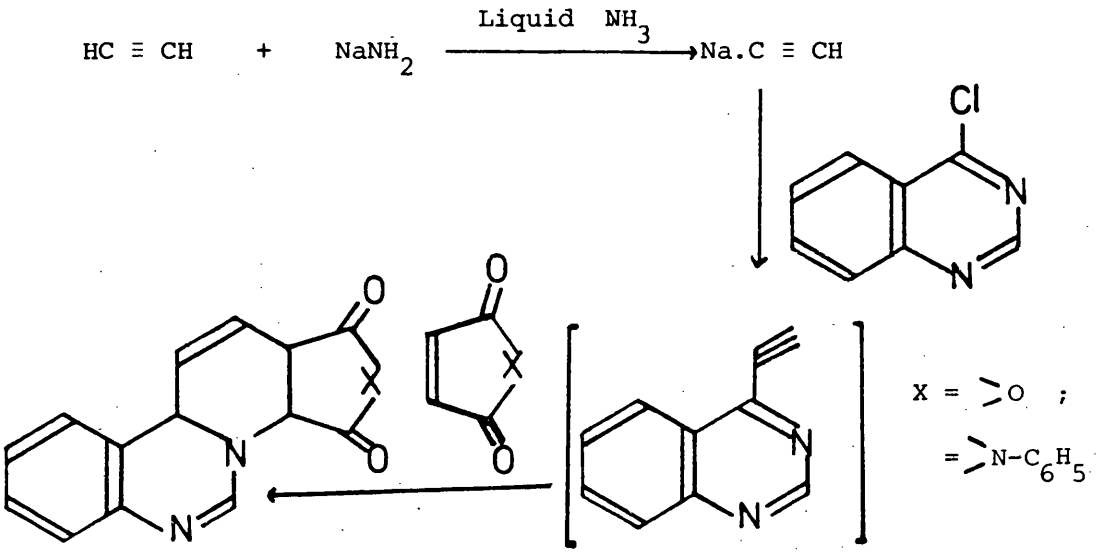


N-phenylmaleimide or maleic anhydride as dienophile, a crude mixture of decomposition products was obtained each time. The failure of the reaction may be due to the highly reactive, acid-labile nature of the starting material, 4-chloroquinazoline.

Methods involving the preparation of an acetylide in liquid ammonia, and the reaction of which in situ with 4-chloroquinazoline, may yield the intermediate required

for reaction with dienophiles to furnish di- and tri-azasteroids, (see Scheme 69).

Scheme 69

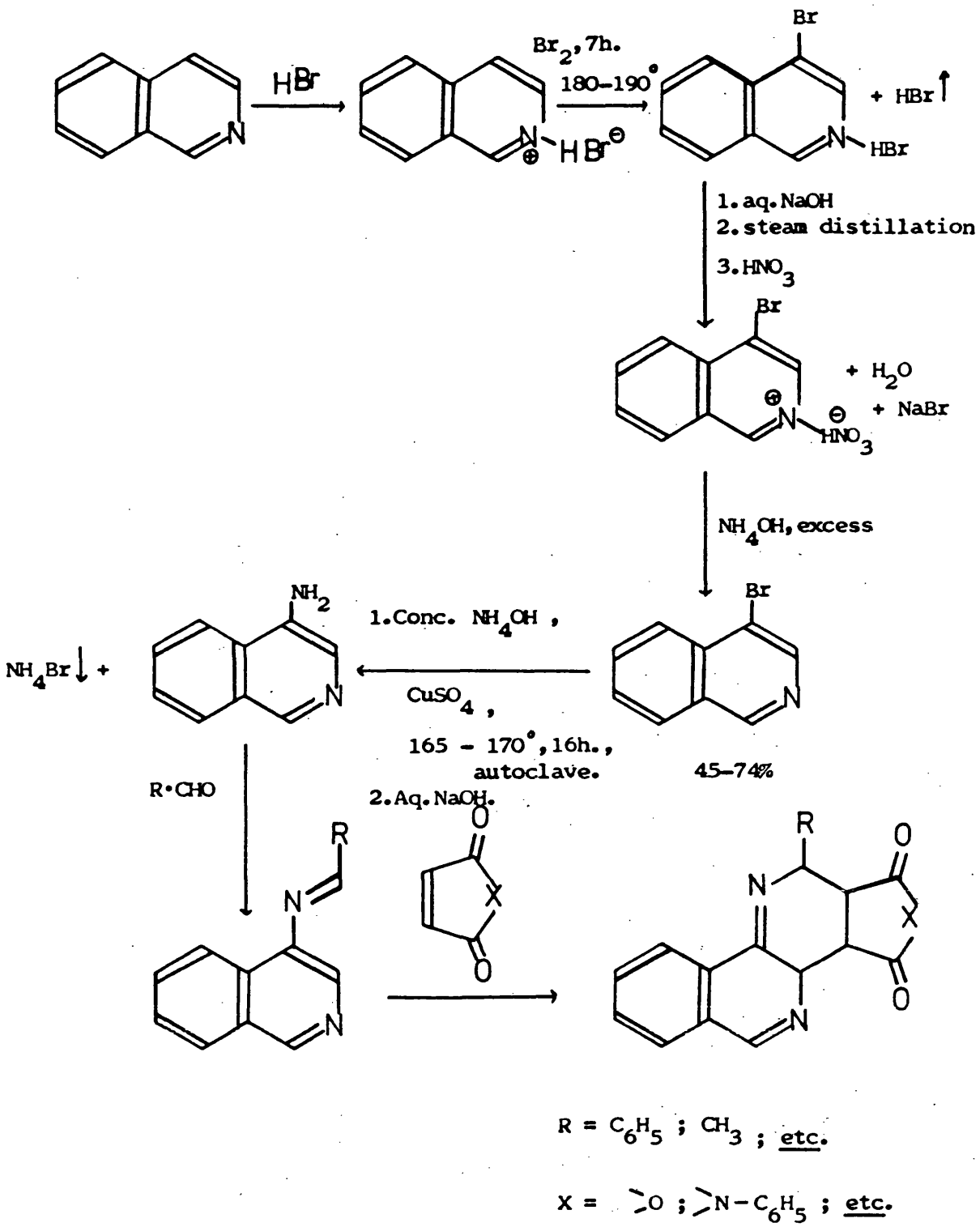


Further work is necessary to establish the synthetic value of this reaction.

8.2.2 Synthesis of nitrogen-containing steroidal compounds from isoquinoline derivatives

It may be possible to synthesize di- and tri-azasteroids via 4-amino- and 1-amino-isoquinoline, (see Schemes 70 and 71, respectively).

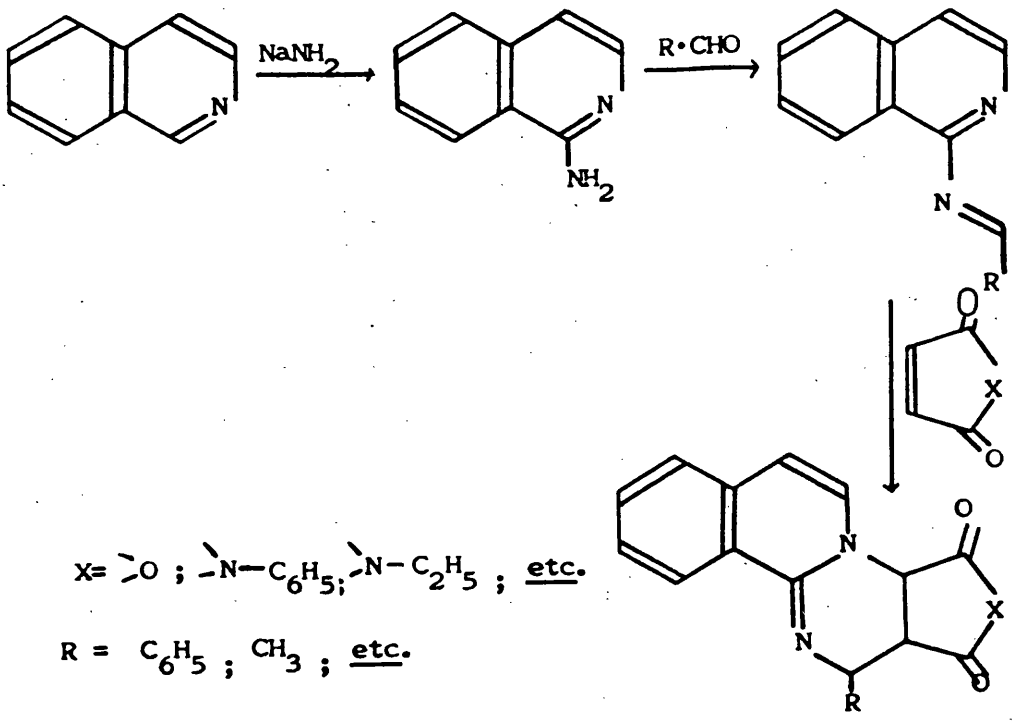
Scheme 70



R = C_6H_5 ; CH_3 ; etc.

X = >O ; >N–C_6H_5 ; etc.

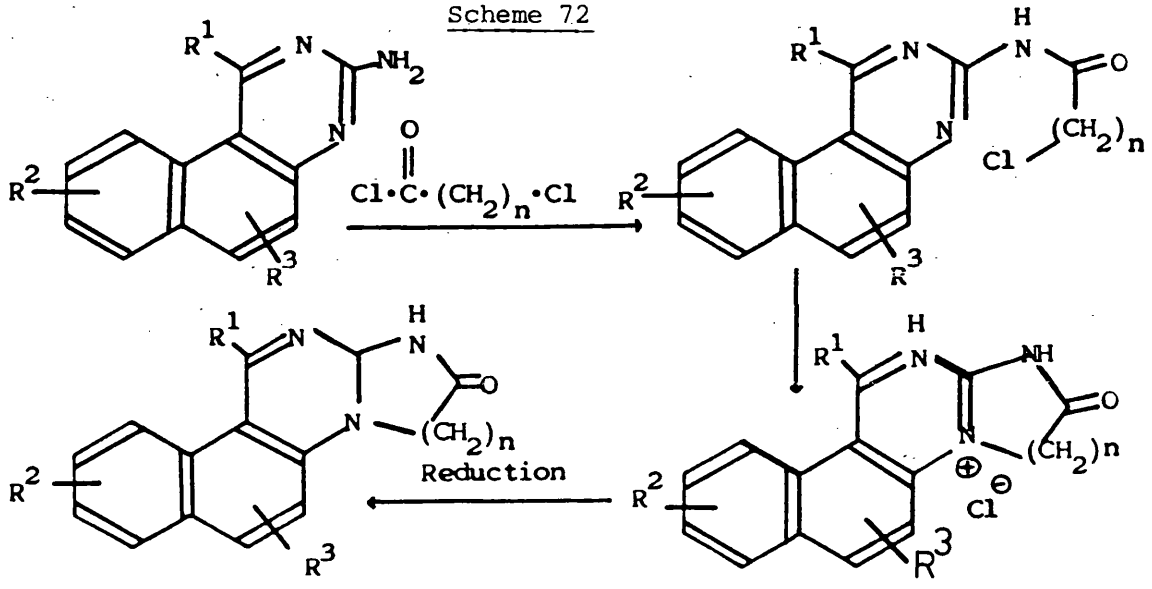
Scheme 71



8.2.3 Synthesis of N-containing steroids from substituted naphthalenes

The reaction of 3-aminobenzo [f] quinazoline with a series of chloroalkyl-chlorides may lead to a range of triazasteroids, (see Scheme 72). Introduction of methoxy, phenoxy, halo, or alkyl substituents in rings A and/or B of the steroid skeleton, may yield compounds with a variety of potentially interesting pharmacological properties.

Scheme 72



PART III

EXPERIMENTAL

Analysis of compounds

Infra-red spectra were recorded as stated, on a Perkin-Elmer 237 grating spectrophotometer, or a Pye Unicam SP.200 spectrophotometer.
Ultra-violet absorption spectra were measured in the solutions stated, with a Perkin-Elmer 402 spectrophotometer or a Perkin-Elmer 124 double beam ultra-violet spectrophotometer, in matched 1cm. silica cells.
Proton magnetic resonance spectra were recorded on a J.E.O.L. P.S.100 nuclear magnetic resonance spectrometer operating at 100 MHz and 2.349 Tesla, or a Varian A60, 60 MHz spectrometer, using tetramethyl silane as internal reference, in the solvents stated.
Carbon-13 magnetic resonance spectra were recorded on a J.E.O.L. FX 90Q Fourier Transform nuclear magnetic resonance spectrometer, operating at a frequency of 22.5 MHz, using tetramethyl silane and a deuterated solvent as internal locks.
Mass spectra were recorded at 70 eV with an A.E.I. single focussing mass spectrometer or an A.E.I. high resolution MS50 mass spectrometer.

Elemental analyses were carried out at the microanalytical laboratories in Oxford (Dr. F.B. Strauss) and London (G.S. Crouch, Esq.), and in Organon Laboratories (Newhouse).
Analytical and preparative thin layer chromatography (T.l.c.) was carried out on silica gel ($60F_{254}$ or 60) plates [Merck], or aluminium oxide ($60F_{254}$ or 60) neutral type E plates [Merck].
Column chromatography was performed on silica gel m.f.c., alumina H m.f.c., or aluminium oxide m.f.c. (neutral or acidic) [Hopkin and Williams].

T.l.c. plates were examined under visible and ultra-violet light (λ_{365nm} and λ_{254nm}). Staining reagents used to develop plates:- iodine, sulphuric acid(4%) in methanol, or ethanolic solution of 2,4-dinitrophenylhydrazine.

Thin Layer Chromatography (T.l.c.)

Solvent systems employed for elution:-

Solvent A. - Toluene/Ethyl acetate (85:15)

Solvent B. - Toluene/Ethyl acetate (1:1)

Solvent C. - Chloroform(100%)

Solvent D. - Pentane/Chloroform (1:1)

Solvent E. - Toluene/Chloroform (6:4)

Solvent F. - Toluene/Chloroform (9:1)

Solvent G. - Dichloromethane/Methanol/Water (95:4:1)

Solvent H. - Dichloromethane/Diethyl Ether/Methanol (75:20:5)

Solvent I. - Chloroform/Acetone/Methanol/Ammonium hydroxide(10:3:2:0.3)

Solvent J. - Dichloromethane/Diethyl ether/Methanol/Water(76:15:8:1)

Solvent K. - Dichloromethane/Acetone (3:2)

Solvent L. - Chloroform/Methanol/Acetic acid (95:5:5).

Melting points were recorded on a Gallenkamp melting-point apparatus, Kofler Hotstage, or a microscope fitted with a hotstage.

All melting points and boiling points are uncorrected.

PART III EXPERIMENTAL (CONTINUED)

CHAPTER NINE

SYNTHESIS OF AZASTEROIDS FROM SUBSTITUTED ISOQUINOLINES VIA THE DIELS-ALDER REACTION

9.1 Isoquinoline methiodide(381)

Isoquinoline(258g, 2M) and iodomethane(284g, 2M) were dissolved in methanol (500 ml) with cooling in an ice-bath. On allowing to stand overnight, a bright yellow, crystalline product precipitated. This was collected by filtration. The mother liquor was evaporated, under reduced pressure to low volume, resulting in further precipitation of product. The product was washed with cold methanol, dried and weighed (530g, 97.8%), m.p. 159° (lit.[501] 159°).

^{1}H nmr$_{(CF_3COOH)}$ δ 9.64(1H,s,C_1-H); 8.7-8.0(6H,m,aromatic protons); 4.26(3H,s,$\equiv\overset{\oplus}{N}$-$CH_3$)ppm.

Mass Spec. 142,129 m/e.

9.2 2-Methylisoquinol-1-one(382) via the oxidation of (381)

Isoquinoline methiodide (30g, 0.11M) was dissolved in water (500 ml). After the addition of a cooled solution of potassium hydroxide (24.8g, 0.44M) in water (150 ml), an aqueous solution (300 ml) of potassium ferricyanide (73.1g, 0.22M) was added. The resulting thick yellow emulsion was stirred for 2 h. at 25°. The product was extracted with benzene (4 x 100 ml), washed with water (2 x 60 ml), dried over anhydrous magnesium sulphate, and finally the solvent removed under reduced pressure to yield a

red oil (16.8g, 95.4%). Distillation of the red oil under reduced pressure afforded a yellow oil, which on standing, formed platelets of low m.p. (26°). The red oil was sufficiently pure to react further, thus making the final distillation step unnecessary in most cases.

ν_{max} (neat film)	3,500; 3,050; 2,925; 1,640 (>C=O); 1,490; 790 cm^{-1}.
^1H nmr δ ($CDCl_3$)	8.3-8.45(1H,m,C_8-H); 7.25-7.5(3H,m, $C_{5,6,7}$-H's); 6.82-6.92[1H,d(J=8Hz), C_3-H]; 6.2-6.3[1H,d(J=8Hz), C_4-H]; 3.4(3H,s,>N-CH_3) ppm.
Mass Spec.	159(M^+) m/e units.
Elemental Analysis:-	$C_{10}H_9NO$ requires C,75.47%; H,5.66%; N,8.81%.
	found C,75.52%; H,5.67%; N,8.84%.

(See Appendix II for Carbon-13 spectral data).

9.3 2-Methylisoquinol-1-one-4-mercuric acetate(383)

To a solution of mercuric acetate (6.5g) in glacial acetic acid[502,503] (200 ml), 2-methylisoquinol-1-one (3.3g) was added. The resulting yellow solution was stirred for 18 h. at 25°. Removal of the acid under reduced pressure gave an almost colourless solid. Recrystallization of the crude product from absolute ethanol yielded colourless needles (8.2g, 94.6%); m.p. 218-220°.

ν_{max}(liquid paraffin)	3,400; 1,620; 1,570; 1,300 cm^{-1}.
^1H nmr $\delta_{(CD_3)_2SO}$	8.4(1H,d,C_8-H); 7.4-7.75(3H,m,$C_{5,6,7}$-H's); 7.18(1H,s,C_3-H); 3.6(3H,s,>N-CH_3); 2.06(3H,s,CH_3:C=O) ppm.
Mass Spec.	417(M^+); 158 m/e.
Elemental Analysis:-	$C_{12}H_{11}NO_3Hg$ requires C,34.5%; H,2·6%; N,3.4%
	found C,34.5%; H,2.6%; N,3.3%

9.4.1 Methyl trans 3'[4(2-methyl-4-oxo-1-isoquinolyl]propenoate(384)

Methyl cyanide (30 ml) was added to a mixture of dried 2-methylisoquinol-1-one-4-mercuric acetate(383) (4.18g, 10 mM) and palladium II acetate (2.25g, 10 mM). The resulting brown-green emulsion was stirred for 0.5 h. at 25°, after which an excess of methyl acrylate (1.72g, 20 mM) was added dropwise. The black suspension thus formed was stirred for 48 h. at 25°. The black suspension was then filtered by suction through a Celite bed (3 cm depth) on a sinter. The Celite was carefully rinsed with chloroform (300 ml). The yellow filtrates were combined, and after removal of the solvents under reduced pressure, the off-white solid was crystallised from methanol to give colourless crystals (2.1g, 87.5%), m.p. 172° of the required diene(384).

ν_{max}(liquid paraffin)	1,720; 1,680; 1,625; 1,580; 1,195 cm^{-1}.
^1H nmr δ_{CDCl_3}	8.35-8.55(1H,d,C_8-H); 7.96[1H,d(J=15Hz), C_9-H]; 7.35-7.80(4H,m,$C_{3,5,6,7}$-H's); 6.30[1H,d(J=15Hz),C_{10}-H]; 3.83(3H,s,-OCH_3); 3.65(3H,s,>N-CH_3) ppm.

Mass Spec. 243(M^+); 212; 184 m/e.

Elemental Analysis:- $C_{14}H_{13}NO_3$ requires C,69.1%; H,5.4%, N,5.8%

found C,69.2%; H,5.4%; N, 5.8%

9.4.2 Ethyl-trans 3'[4(2-methyl-4-oxo-1-isoquinolyl)] propenoate(385)

To a mixture of 2-methylisoquinol-1-one-4-mercuric acetate(383) (2.09g, 5mM) and palladium II acetate (1.13g, 5 mM), methyl cyanide (20 ml) was added. The dark green emulsion was stirred for 0.25 h. at 25°, after which an excess of ethyl acrylate (1.0g, 10 mM) was added. The resulting black suspension was stirred for 16 h. at 25°, and then filtered through a 'Celite' bed (4 cm depth) on a sinter. After careful washing of the celite with chloroform, the yellow filtrates were combined and the solvents removed under reduced pressure to afford a yellow oily solid. The yellow solid was crystallised from ethanol to give almost colourless crystals (0.9g, 70.3%), m.p. 187° of the diene(385).

$\nu_{max(Nujol)}$ 1,700; 1,685; 1,625; 1,560 cm^{-1}.

^1H nmr δ_{CDCl_3} 8.45-8.62(1H,d,C_8-H); 7.91-8.12(1H,d[J=16Hz], C_9-H); 7.40-7.90(4H,m,$C_{3,5,6,7}$-aromatic protons); 6.28-6.41(1H,d[J=16Hz],C_{10}-H); 4.16-4.52(2H,q,-CH_2); 3.62(3H,s,>N-CH_3); 1.29-1.52(3H,t,-CH_3) ppm.

Mass Spec. 257(M^+) m/e.

Elemental Analysis:- $C_{15}H_{15}NO_3$ requires C,70.0%; H,5.8%; N,5.5%

found C,70.2%; H,5.8%; N,5.5%.

9.5 Preparation of dienophiles

9.5.1 Preparation of N-phenylmaleimide(387)

To a stirred, refluxing solution of maleic anhydride (49.0g, 0.5M) in diethyl ether (600 ml), a solution of aniline (46.5g, 0.5M) in diethyl ether (50 ml) was added dropwise through a dropping funnel. The resulting suspension was stirred at 25° for 0.5 h. After cooling in an ice-bath, the off-white precipitate was isolated by suction filtration. The cream-coloured amide-acid intermediate(387A)(83.0g, 86.9%), m.p. 202°, was cyclized without further purification.

To a mixture of acetic anhydride (170 ml) and anhydrous sodium acetate (20.5g), the maleanilic acid(387A) (48.0g) was added. The resulting pale yellow suspension was stirred whilst heating on a steam bath for ca. 0.5 h. until a solution formed. The reaction mixture was cooled in a water bath (20°) and then poured into ice water (300 ml). The yellow precipitate which formed, was isolated by suction filtration, washed with ice-cold water (3 x 100 ml) and then with petroleum ether (b.p. 30-40°) (2 x 50 ml), and finally dried in an oven at 60° overnight to give a pale yellow powder (37.5g, 86.7%), m.p. 88-90°. Recrystallization from cyclohexane afforded bright yellow needles(387), m.p. 90°.[504]

^{1}H nmr δ_{CDCl_3} 7.20-7.60[5H,m,aromatic protons];
6.80[2H,s,-CH=CH-]ppm.

Mass Spec. 173(M^+) m/e.

9.5.2 Preparation of N-benzylmaleimide(388)

To a stirred, gently refluxing solution of maleic anhydride (49.0g, 0.5M) in diethyl ether (850 ml), benzylamine (53.5g, 0.5M) in diethyl ether (70 ml) was added dropwise through a dropping funnel. The resulting white emulsion was stirred for a further 2.0 h. at 25°. After cooling the reaction mixture in an ice bath, followed by filtration, the white powder(388A) thus obtained was dried, then cyclised without further purification.

To a stirred mixture of acetic anhydride (150 ml) and sodium acetate (20.5g, 0.25M), the intermediate(388A) (51.25g, 0.25M) was added. The resulting white emulsion was stirred on a steam bath for 0.5 h. The brown solution thus formed was cooled to 25° then poured into ice water (200 ml). The pale brown precipitate thus formed was filtered under suction, washed with ice-cold water (2 x 100 ml), then with petroleum ether (b.p. 30-40°) (2 x 50 ml.) to afford off-white crystals (39.5g, 84.49%) which on recrystallization from cyclohexane gave colourless needles(388), m.p. 64-65°.

^{1}H nmr δ_{CDCl_3} 7.2-7.4(5H,m,aromatic protons); 6.6(2H,s, -C<u>H</u>=C<u>H</u>-); 4.6(2H,s,-C<u>H</u>$_2$-) ppm.

Mass Spec. 187(M^+) m/e.

Elemental Analysis:- $C_{11}H_9O_2N$ requires C,70.6%; H,4.8%; N,7.5%

found C,70.5%; H,5.0%; N,7.4%

(See Appendix 11 for Carbon-13 spectral data).

9.5.3 Attempted preparation of maleimide(389) from N-benzylmaleimide(388)

A solution of N-benzylmaleimide (18.0g) in methanol (200 ml) was added to the catalyst (5% palladium/charcoal) (1.0g). The mixture was placed in a hydrogenator (pressure = 100 $lb/in.^2$) and shaken at 25° for 12 h. The resulting black solution was filtered through a Celite bed (3 cm depth) on a sinter to remove the palladium and charcoal. On removal of the solvent from the green solution under reduced pressure, a white solid was obtained. Recrystallization of this solid from benzene afforded colourless platelets of a pure product(390) (15.9g, 87.4%), m.p. 84°, which was not the required product(389).

^{1}H nmr δ_{CDCl_3} 7.2-7.4(5H,m,aromatic protons); 4.6(2H,s, N-C$\underline{H}_2$-); 2.66(4H,s,-C$\underline{H}_2$-C$\underline{H}_2$-) ppm.

Mass Spec. 189(M^+) m/e.

Elemental Analysis:- $C_{11}H_{11}NO_2$ requires C,69.8%; H,5.8%; N,7.4%

found C,69.5%; H,5.8%; N,7.2%.

(See Appendix 11 for Carbon-13 spectral data).

9.5.4 Preparation of N-ethylmaleimide(391)

To a stirred solution of maleic anhydride (24.5g, 0.25M) in diethyl ether (400 ml), ethylamine (11.3g, 0.25M) in diethyl ether (30 ml) was added dropwise. The resulting off-white emulsion was stirred for 1.5 h. at 25°. After cooling the reaction mixture in an ice bath, followed by suction filtration, the white intermediate (391A) (29.5g, 82.5%) thus obtained, was dried, then used in the final step without further purification.

To a stirred mixture of acetic anhydride (100 ml) and sodium acetate (16.4g, 0.2M), the intermediate(391A) (28.6g, 0.2M) was added. The white emulsion was stirred under reflux, on a steam bath for 0.5 h. After cooling in an ice bath, the yellow solution was poured into ice-water (80 ml). On allowing to stand for 2.0 h., the white precipitate which formed, was isolated by suction filtration to yield the required product(391) (22.6g, 90.4%), m.p. 44-46°. After washing with ice-water (2 x 30 ml) and petroleum ether (b.p. 30-40°) (2 x 40 ml), the white powder was recrystallised from cyclohexane to afford colourless crystals, m.p. 46°.

^{1}H nmr δ_{CDCl_3}	6.70(2H,s,-HC=CH-); 3.40-3.70(2H,q,-CH_2-); 1.05-1.25(3H,t,-CH_3) ppm.
Mass Spec.	125(M^+) m/e

9.5.5.1 Preparation of 5,5-diphenylhydantoin(392)[505]

This compound(392) was prepared by condensing benzil with urea, as described in the text by Vogel.[505]

Yield	58%, m.p. 297-298°.
ν_{max}	3,300(-OH); 1,730(>C=O) cm^{-1}.
^{1}H nmr $\delta_{CDCl_3/(CD_3)_2SO}$	11.00(1H,s,-OH); 8.98(1H,s,-OH); 7.20-7.60(10H,m,aromatic protons) ppm.
Mass Spec.	252(M^+) m/e.

(See Appendix 11 for Carbon-13 spectral data).

9.5.5.2 Attempted O-methylation of the hydantoin(392)

To a white suspension of hydantoin(392) (3.0g) in ethanol (50 ml), an ethanolic solution of potassium hydroxide (0.6g in 50 ml) was added. Methyl iodide (6.0g) was added dropwise to the resulting colourless solution, under an atmosphere of nitrogen. The mixture was stirred under reflux for 6 h. The yellow suspension thus formed, was poured into ice-water (100 ml) giving a solution of pH = 6. The product precipitated on basifying the solution to pH = 11, by dropwise addition of sodium hydroxide (5M, ca. 2 ml). Suction filtration, followed by washing with water (10 ml), afforded a white powder (2.9g, 93.5%), m.p. 185°, which was not the required product(393). The product was found to be the N-methylated hydantoin(394).

ν_{max}	3,450(-OH); 1,790; 1,720(>C=O); 1,160(C-O-C); 1,100(C-O-C) cm^{-1}.
^1H nmr $\delta_{CDCl_3/(CD_3)_2SO}$	9.15(1H,s,-OH); 7.20-7.55(10H,m,aromatic protons); 3.00(3H,s,>N-C$\underline{H}_3$) ppm.
Mass Spec.	266(M^+); 251 m/e.

9.5.6 Preparation of 2-ethoxypyrroline(395)[506]

To the pale-green solution formed by dissolving triethyloxonium fluoroborate(25g) in dichloromethane (100 ml) under an atmosphere of nitrogen at 0°, 2-pyrrolidinone (11.2g) was added dropwise via an addition funnel. The mixture was stirred at 25° for 12 h. under an atmosphere of nitrogen. The resulting dark-

yellow solution was slowly poured into cooled, saturated aqueous sodium carbonate solution (20 ml). After stirring the mixture vigorously for 1 h., the organic layer was separated, washed with saturated sodium carbonate solution (2 x 10 ml), dried over anhydrous magnesium sulphate, and finally, the solvent removed under reduced pressure. The product was distilled under reduced pressure (10 mm Hg), using a Vigreux column (15 cm) to yield a colourless liquid (8.4g, 56.4 % based on 2-pyrrolidinone).

$\nu_{max(Nujol)}$	1,655; 1,375; 1,335; 1,309; 1,030 cm^{-1}
^1H nmr δ_{neat}	4.2(2H,q,-C$\underline{H}_2$-); 3.3(2H,t,>C$\underline{H}_2$); 2.2(4H,m,[>C$\underline{H}_2$]$_2$); 1.2(3H,t,-C$\underline{H}_3$) ppm.
Mass Spec.	113(M^+) m/e.

9.5.7 Preparation of Imidoyl Chlorides(397)

The imidoyl chlorides were prepared by reacting the amide (1 equivalent) with phosphorus oxychloride (2 equivalents) in benzene. The mixture was allowed to stir at 0^o for 3 h. under an atmosphere of nitrogen, before addition of the diene dissolved in a suitable solvent.

9.6.1 Reaction of diene(384) with acrylic acid to obtain adduct(398)

The diene(384) (100 mg) was dissolved in acetonitrile (10 ml). After the addition of acrylic acid (1.5 ml) in excess, the colourless solution was stirred under reflux for 8 h. The solvent and excess reagent (acrylic acid) was removed under reduced pressure to afford

a white solid. The solid was washed with ether and then recrystallised from acetic acid to yield colourless crystals (106 mg, 82%), m.p. 223-225°.

$\nu_{max(Nujol)}$ 2,800(-OH); 1,740(>C=O); 1,640(>C=O) cm^{-1}.

^1H nmr $\delta_{(CD_3)_2 \cdot SO}$ 7.10-8.00(4H,m,aromatic protons); 6.20-6.70(1H,m,olefinic proton); 2.00-4.60(5H,m,aliphatic protons); 3.65(3H,s,-O-C$\underline{H}_3$);3.00(3H,s,>N-C$\underline{H}_3$) ppm.

Mass Spec. 315(M^+) m/e

Elemental Analysis:- $C_{17}H_{17}NO_5$ requires C,64.8% H,5.4%, N,4.4%

found C,64.9%; H,5.3%; N,4.5%.

9.6.2 <u>Reaction of diene(384) with maleic anhydride to obtain methyl 1,3,3a,3b,4,5,11,11a-octahydro-4-methyl 1,3,5-trioxofuro[3,4-c] phenanthridine-11-carboxylate(399)</u>

To a solution of the diene(384) (1.0g) in acetonitrile (50 ml), maleic anhydride (0.8g) in excess was added. The resulting mixture was stirred under reflux for 12 h. The lemon-yellow solution was cooled in an ice-bath to afford colourless crystals, which were purified by washing with acetonitrile to yield product (399) (1.28g, 91.4%), m.p. 244-246°.

λ_{max} 250,335 nm

$\nu_{max(Nujol)}$ 1,800(>C=O); 1,770(>C=O); 1,755(>C=O); 1,670(>C=O); 1,230 cm^{-1}.

^1H nmr $\delta_{(CD_3)_2 \cdot SO}$ 7.85-8.09(2H,m,$C_{6,7}$-H's); 7.34-7.65(2H,m, $C_{8,9}$-H's); 7.00-7.15(1H,m,C_{10}-H); 4.60(1H,m, C_{3b}-H); 3.95-4.25(2H,m,$C_{3a,11a}$-H's); 3.79(3H,s,-O.C$\underline{H}_3$); 3.62(1H,m,C_{11}-H); 3.12(3H,s,>N-C$\underline{H}_3$) ppm.

Mass Spec. 341(M^+) m/e.

Elemental Analysis:- $C_{18}H_{15}NO_6$ requires C,63.3%; H,4.4%; N,4.1%

found C,63.0%; H,4.4%; N,4.1%.

9.6.3 Methyl-2,3,3a,3b,4,5,11,11a-octahydro-4-methyl-1,3,5-trioxo-1H-cyclopenta[c]phenanthridine-11-carboxylate(400).

4-Cyclopentene-1,3-dione(0.4g) was added to a solution of the diene(384) (0.5g) in acetonitrile (20 ml). The mixture was stirred under reflux for 12 h. On cooling the intense yellow solution, a pale orange product precipitated. The precipitate was washed with acetonitrile and dried, to yield a yellow/orange microcrystalline product(400) (0.63g, 91.3%), m.p. 254-255°.

ν_{max}(Nujol) 1,755(>C=O); 1,705(>C=O); 1,650; 1,610; 1,220 cm^{-1}.

^1H nmr $\delta_{(CD_3)_2 \cdot SO}$ 7.2-8.0(4H,m,$C_{6,7,8,9}$-aromatic protons); 6.8-7.0(1H,m,C_{10}-H); 4.38-4.55(1H,m,C_{3b}-H); 3.5-4.0(2H,m,$C_{3a,11a}$-H's); 3.70(3H,s,-OCH_3); 3.50-3.65(1H,m,C_{11}-H); 3.25-3.40(2H,m,C_2-H's); 3.10(3H,s,>N-CH_3) ppm.

Mass Spec. 339(M^+) m/e.

Elemental Analysis:- $C_{19}H_{17}O_5N$ requires C,67.3%; H,5.0%; N,4.1%

found C,67.2%; H,5.0%; N,4.2%.

9.6.4 Methyl-2,3,3a,3b,4,5,11,11a-octahydro-4-methyl-1,3,5-trioxo-2-phenyl-1H-pyrrolo[3,4-c]-phenanthridine-11-carboxylate(401)

9.6.4.1

The diene(384) (0.5g) was dissolved in acetonitrile (30 ml). N-Phenylmaleimide (0.71g) was added and the resulting yellow solution stirred under reflux for 24 h. The product which crystallised in the mother liquor was filtered off, washed with acetonitrile, and finally dried to afford colourless microcrystals of the required adduct(401), (0.74g, 86.4%), m.p. 259-260°.

λ_{max}	266; 338 nm
ν_{max} (KCl disc)	1,750(>C=O); 1,700(>C=O); 1,640(>C=O); 1,600; 1,495; 1,400 cm^{-1}.
^1H nmr $\delta_{(CD_3)_2 \cdot SO}$	7.88-8.10(2H,m,$C_{6,7}$-H's); 7.20-7.65 (5H,m,>N-C_6H_5 aromatic protons); 7.00-7.20 (1H,m,C_{10}-H); 6.60-6.80(2H,m,$C_{8,9}$-H's); 4.59-4.75(1H,m,C_{3b}-H); 3.85-4.10(2H,m,$C_{3a,11a}$-H's); 3.75(3H,s,O-CH_3); 3.50-3.70(1H,m,C_{11}-H); 3.18(3H,s,>N-CH_3) ppm.
Mass Spec.	416(M^+) m/e.
Elemental Analysis:-	$C_{24}H_{20}O_5N_2$ requires C,69.2%; H,4.8%; N,6.7%
	found C,69.1%; H,4.7%; N,6.8%.

9.6.4.2

To a suspension of the adduct(399) (0.34g) in sodium-dried benzene (50 ml), freshly distilled aniline (0.4 ml) was added. The resulting cloudy solution was refluxed, employing a 'Dean-

Stark separator', for 15 h. After removal of the solvent (benzene) under reduced pressure, the yellow oil was titurated with diethyl ether to afford a white solid. Suction filtration, followed by washing with diethyl ether gave a white powder (0.21g, 50.7%), m.p. 259-260°, which was found to be identical to product (401) by spectroscopy and thin layer chromatography.

9.6.5 Reaction of diene(384) with 'p'-benzoquinone

The yellow solution formed by dissolving the diene ester (384) (0.10g) and 'p'-benzoquinone (0.16g) in glacial acetic acid (15 ml), was heated for 3 h. under reflux. After removal of the solvent by distillation under reduced pressure, the dark yellow solid was carefully washed with methanol (2 ml) and acetonitrile (2 ml) to afford a pale yellow powder (0.06g, 42.8%), m.p. 259°, of the adduct (402).

$\nu_{max_{(Nujol)}}$ 1,710(>C=O); 1,660(>C=O) cm^{-1}.

^1H nmr δ_{CDCl_3} 9.10-7.60(5H,m,$C_{7,8,9,10,11}$-aromatic protons); 7.29(2H,s,$C_{2,3}$-olefinic protons); 3.72(3H,s, -O·C$\underline{H}_3$); 3.12(3H,s,>N-C$\underline{H}_3$) ppm.

Mass Spec. 347(M^+) m/e.

Elemental Analysis:- $C_{20}H_{13}O_5N$ requires C,69.2%; H,3.8%; N,4.0%

found C,69.5%; H,3.8%; N,4.2%

9.6.6 Preparation of adduct(403) *via* the reaction of diene(384) with 1,4-naphthoquinone

To a solution of the diene(384) (0.24g) in acetonitrile (30 ml), 1,4-naphthoquinone (0.31g) freshly recrystallised from petroleum ether (b.p. 60-80°), was added. The resulting green solution was refluxed for 24 h. The green crystals which formed on cooling the mother liquor in an ice-bath, were filtered off, washed with petroleum ether (b.p. 60-80°) and acetonitrile, and finally dried at 100° overnight to afford pale green crystals of the product(403) (0.35g, 89.7%), m.p. 302-305°.

$\nu_{max(Nujol)}$ 1,720(>C=O), 1,665(>C=O); 1,348; 1,304 cm^{-1}.

Proton nmr could not be recorded as the product was extremely insoluble in the usual solvents (dimethylsulphoxide, trifluoroacetic acid, *etc.*)

Mass Spec. 397(M^+); 380 m/e

Elemental Analysis:- $C_{24}H_{15}NO_5$ requires C,72.5%; H,3.8%; N,3.5%

found C,72.3%; H,3.7%; N,3.6%.

9.6.7 Reaction of diene(384) with diethyl azodicarboxylate

The diene(384) (0.20g) and diethyl azodicarboxylate (0.57g) were dissolved in acetonitrile (15 ml). The yellow solution was refluxed for 24 h. The solvent (acetonitrile) was removed under reduced pressure to give a pale yellow oil. Attempts to completely remove the excess reagent (diethyl azodicarboxylate) by distillation at 100° and low pressure (0.1 mm Hg) were not

successful. At temperatures greater than 100°, decomposition of product (404) occurs (as observed by thin layer chromatography). Attempts to purify the product by column chromatography were unsuccessful (decomposition of product (404) occurred when either a silica or alumina column was employed).

Complete loss of starting material was not achieved even after heating the reaction mixture under reflux for 68h. The product could not be crystallized satisfactorily from methanol, acetonitrile, ether, etc. However, pale yellow platelets, m.p. 164-168° (0.08g), were obtained from diethyl ether.

T.l.c. on silica (chloroform elution)	R_f = 0.06 (product (404))
	R_f = 0.22 (diene (384))
	R_f = 0.66 (diethyl azodicarboxylate)
ν_{max} (Nujol)	1,750(>C=O); 1,650(>C=O) cm^{-1}.
^1H nmr δ_{CDCl_3}	7.1-8.5(5H,m,aromatic protons); 4.78 (1H,m,C_1-H); 4.20(4H,m,2-CH_2-); 3.88(1H,s,C_{3a}-H); 3.73(3H,s,-O-CH_3); 3.26(3H,s,>N-CH_3); 1.20-1.40(6H,m,2-CH_3) ppm.
Mass Spec.	417(M^+) m/e.

9.6.8.1 Reaction of diene(384) with N-benzylmaleimide

To a solution of the diene(384) (0.50g) in acetonitrile (30 ml), N-benzylmaleimide (1.50g) was added. The resulting yellow solution was refluxed for 96 h. On cooling, the grey-white solid which formed, was isolated by filtration, washed with acetonitrile (10 ml) and methanol (10 ml) to afford a colourless microcrystalline product (405) (0.73g, 57.5%), m.p. 314-315°.

$\nu_{max_{(Nujol)}}$	1,762(>C=O); 1,730(>C=O); 1,715(>C=O); 1,660(>C=O); 1,615; 1,170 cm^{-1}
^1H nmr $\delta_{(CD_3)_2.SO}$	6.70-8.01(13H,4multiplets and 1 singlet, aromatic protons); 4.20-4.53(5H,m,2[>N-C$\underline{H}_2$-] and C_{3b}-$\underline{H}$); 1.40-4.60(7H,broad,$C_{3a,8b,11a,11b,12,12a,15}$-aliphatic protons); 3.70(3H,s,O-C$\underline{H}_3$); 3.09(3H,s,>N-C$\underline{H}_3$) ppm.
Mass Spec.	632, 615, 555 m/e.
$C_{36}H_{31}O_7N_3.H_2O$	requires C,68.0%; H,5.2%; N,6.6%
	found C,67.9%; H,5.2%; N,6.7%

9.6.8.2 Attempted preparation of adduct(406)

9.6.8.2.1

The diene(384)(1 equivalent) was heated under reflux with N-benzyl maleimide (1 equivalent) in acetonitrile for 96 h. On cooling, no product was isolated. Starting material(384) was recovered. Examination by T.l.c. on a silica plate showed absence of any new product.

9.6.8.2.2

The adduct (399) (0.5g, 1 equivalent) was heated under reflux with benzylamine (4 equivalents) in sodium-dried benzene (40 ml) under a 'Dean-Stark separator' for 48h. The reaction was followed by T.l.c. on a silica plate. Although complete loss of starting material (399) was observed, proton nmr of the crude reaction mixture indicated that decomposition of starting material (399) had occurred.

9.6.9 Reaction of the adduct(399) with sodium acetate in acetic anhydride

The adduct(399) (0.5g) was dissolved in acetic anhydride (16 ml). After the addition of anhydrous sodium acetate (0.6g), the mixture was heated on a steam bath for 0.5 h. The resulting yellow solution was poured into ice-water (10 ml), extracted with chloroform (2 x 30 ml), and the chloroform extract washed with aqueous, saturated sodium bicarbonate solution (10 ml) followed by water (2 x 10 ml). Removal of the solvent (chloroform) under reduced pressure, afforded a white solid (0.26g, 55%), m.p. 84-86° of the amide(407). The product (407) was recrystallised from water.

ν_{max} (KBr disc) 3,500; 2,700-3,200(—COOH); 1,715(>C=O); 1,680; 1,620; 1,260 cm^{-1}.

^1H nmr $\delta_{(CD_3)_2.SO}$ 9.90(1H, broad singlet,-$CO_2\underline{H}$); 6.95-7.65 (6H,m,aromatic protons); 3.32(1H,s,>N$\underline{H}$); 2.03(3H,s,>N-$C\underline{H}_3$) ppm.

Mass Spec. 325(M^+) m/e.

Elemental Analysis:- $C_{17}H_{11}O_6N$ requires C,62.8%; H,3.4%; N,4.3%

found C,62.6%; H,3.4%; N,4.3%.

9.6.10 Reaction of diene(384) with N-ethylmaleimide

9.6.10.1

To a solution of the diene(384) (0.5g) in acetonitrile (40 ml), N-ethylmaleimide (1.03g) was added. The clear yellow solution was stirred under reflux for 72 h. The pink precipitate which resulted on cooling the mixture in an ice-bath, was isolated by filtration, washed with methanol (20 ml) and acetonitrile (20 ml), to afford an

almost colourless microcrystalline product(408) (0.62g, 61.2%), m.p. 340° (decomp. 325°).

$\nu_{max(Nujol)}$	3,220; 1,780(>C=O); 1,750(>C=O); 1,710; 1,700; 1,640; 1,595 cm^{-1}.
^1H nmr $\delta_{(CD_3)_2SO}$	7.70-7.90(1H,m,aromatic proton); 7.39-7.58 (2H,m,aromatic protons); 4.10-4.38(2H,m, $-C\underline{H}_2-$); 3.70-4.00(2H,m,$-CH_2-$); 3.10-4.00 (8H,complex,aliphatic protons); 3.69(3H,s, $-OC\underline{H}_3$); 3.02(3H,s,$\gtrsim N-C\underline{H}_3$); 0.65-1.05(6H, m,2x$-C\underline{H}_3$) ppm.
Mass Spec.	509, 493(M^+),492,444,431 m/e.
Elemental Analysis:-	$C_{26}H_{27}N_3O_7 \cdot H_2O$ requires C,61.1%; H,5.7%; N,8.2%
	found C,60.8%; H,5.5%; N,8.3%.

9.6.10.2

The above reaction was repeated, employing a 1:1 equivalent of the diene(384) and N-ethylmaleimide, and refluxing the mixture for 96 h. in an attempt to obtain the adduct(409). However, no product could be isolated. Starting material(384) was recovered, together with some degradation products.

9.7.1 Preparation of ethyl 1,3,3a,3b,4,5,11,11a-octahydro-4-methyl-1,3,5-trioxofuro[3,4-c]phenanthridine-11-carboxylate(410) via the reaction of diene(385) with maleic anhydride

To a solution of the diene(385) (1.0g) in acetonitrile (50 ml), maleic anhydride (1.5g) was added. The resulting pale yellow solution was stirred whilst heating under reflux for 24 h. On

cooling the white precipitate which formed was isolated by filtration, washed with ethanol (10 ml) and acetonitrile (10 ml) to afford a colourless microcrystalline product(410), (1.15g, 83.3%), m.p. 239-240°.

ν_{max} (Nujol) 1,885; 1,800; 1,770(>C=O); 1,750(>C=O); 1,670; 1,320; 1,220 cm^{-1}.

^{1}H nmr $\delta_{(CD_3)_2.SO}$ 7.89-8.10(2H,m,$C_{6,7}$-H's); 7.38-7.63(2H,m, $C_{8,9}$-H's); 7.02-7.18(1H,m,C_{10}-H); 4.50-4.70 (1H,m,C_{3b}-H); 3.50-4.40(3H,m,$C_{3a,11,11a}$-H's); 4.09-4.35(2H,q,C_{13}-CH_2); 3.15(3H,s,>N-CH_3); 1.3(3H,t,C_{14}-CH_3) ppm.

Mass Spec. 355(M^+), 310, 283 m/e.

Elemental Analysis:- $C_{19}H_{17}O_6N$ requires C,64.2%; H,4.8%; N,3.9%

found C,64.8%; H,4.8%; N,3.8%.

9.7.2 Reaction of diene(385) with 4-cyclopentene-1,3-dione

The diene(385) (1.0g) was added to a solution of 4-cyclopentene-1,3-dione (1.5g) in acetonitrile (50 ml). The resulting yellow mixture was stirred whilst heating under reflux for 72 h. After cooling the solution in an ice-bath, the resultant dark yellow precipitate was isolated by filtration, washed with acetonitrile (20 ml) and ethanol (20 ml), to afford a yellow microcrystalline product(411) (1.01g, 74%), m.p. 348°-350°.

ν_{max} (Nujol) 1,740(>C=O); 1,730(>C=O); 1,645(>C=O); 1,635(>C=O); 1,600 cm^{-1}.

^{1}H nmr $\delta_{(CD_3)_2 \cdot SO}$ 7.75-8.10(2H,m,aromatic protons); 7.29-7.60 (2H,m,aromatic protons); 6.85-7.02(1H,m, aromatic proton); 4.35-4.60(1H,m,C_{3b}-H); 4.05-4.31(2H,q,C_{13}-CH_2-); 3.25-3.75(5H,m, $C_{3a,11,11a,2,2}$-aliphatic protons); 3.10 (3H,s,>N-CH_3); 1.12-1.33(3H,s,C_{14}-CH_3) ppm.

Mass Spec. 353(M^+), 281, 257, 229, 212, 184 m/e.

Elemental Analysis:- $C_{20}H_{19}NO_5 \cdot 1\frac{1}{2}H_2O$ requires C,63·2%; H,5.8%; N,3.7%

found C,63.0%; H,5.6%; N,3.9%

9.7.3 Reaction of diene(385) with N-phenylmaleimide

9.7.3.1

N-Phenylmaleimide (2.7g) and the diene(385) (1.0g) were dissolved in acetonitrile (40 ml). The yellow-green solution was stirred whilst heating under reflux for 120 h. After cooling in an ice-bath, filtration of the dark-brown suspension afforded a pale-grey product. The solid was washed with acetonitrile (30 ml) and ethanol (20 ml) to give an almost colourless microcrystalline product(412) (0.82g, 35.0%), m.p. 352-354°.

$\nu_{max(Nujol)}$ 1,770(>C=O); 1,735(>C=O); 1,700(>C=O); 1,630 (>C=O); 1,500; 1,460; 1,180; 1,140 cm^{-1}.

^{1}H nmr $\delta_{(CD_3)_2 \cdot SO}$ 6.95-8.02(13H,3 multiplets, aromatic protons); 4.10-4.32(2H,q,C_{14}-CH_2-); 3.25-4.70(8H,m, aliphatic protons); 3.12(3H,s,>N-CH_3); 1.15-1.39 (3H,t,C_{15}-CH_3) ppm.

Mass Spec. 619, 603(M^+), 602, 527, 445 m/e.

Elemental Analysis:- $C_{35}H_{29}N_3O_7 \cdot H_2O$ requires C,67.6%; H,5.0%; N,6.8%

found C,67.7%; H,4.8%; N,6.8%.

9.7.3.2

A solution of the diene(385) (0.5g) and N-phenylmaleimide (0.34g) in acetonitrile (30 ml) was stirred whilst heating under reflux for 120 h. The starting materials were recovered, together with some products of decomposition. Formation of adduct(413) was not observed.

9.8 The attempted reactions of diene(385) with the following dienophiles:-

(i) N-Ethylmaleimide

(ii) N-Benzylmaleimide

(iii) 2-Ethoxypyrroline

(iv) Diethyl azodicarboxylate

(v) 1,4-Naphthoquinone

A mixture of the diene(385) (1 equivalent) and dienophile ((i)→(v)) (4 equivalents) was heated under reflux in acetonitrile for 72 h. In all cases, the expected adduct formation was not observed. Starting material and/or decomposition products were recovered in each case.

9.9 Attempted Diels-Alder reactions of diene(384) with potential dienophiles ((i) → (vii))

(i) 2-Ethoxypyrroline(395)

(ii) 2-Pyrrolidinone

(iii) 1-Methyl-2-pyrrolidinone

(iv) 5,5-Diphenylhydantoin(392)

(v) Methoxyhydantoin(396)

(vi) Imidoyl chloride(397),(R=CH_3), obtained from acetamide

(vii) Imidoyl chloride(397),(R=C_6H_5), obtained from benzamide

To a solution of the diene(384) (1 equivalent) in acetonitrile, the dienophile ((i),(ii),(iii),(iv) or (v)) (4 equivalents) was added. After stirring and heating the mixture under reflux for 72 h., the reaction mixture was examined by T.l.c. on a silica plate.

A solution of the diene(384) (1 equivalent) in acetonitrile, was added to a stirred mixture of the imidoyl chloride((vi) or (vii)) (4 equivalents) in benzene. The resulting mixture was stirred whilst heating under reflux for 48 h. The crude reaction mixture was examined by T.l.c. on a silica plate.

In each of the above seven cases, no adduct formation was observed. Starting materials were recovered from reactions (i),(ii),(iii),(iv) and (v). However, in reactions (vi) and (vii), decomposition of starting material had occurred.

9.10 Attempted formation of diadducts *via* the reaction of diene(384) with two dissimilar dienophiles

9.10.1 Reaction of adduct (399) with *N*-phenylmaleimide.

9.10.2 Reaction of adduct (399) with *N*-benzylmaleimide.

9.10.3 Reaction of adduct (400) with *N*-phenylmaleimide.

9.10.4 Reaction of adduct (401) with maleic anhydride.

9.10.5 Reaction of adduct (401) with 4-cyclopentene-1,3-dione.

General Procedure

To a stirred suspension of the adduct (1 equivalent) in acetonitrile, the dienophile (2 equivalents) was added. The resulting mixture was heated under reflux for 72 h.

In each case, no diadduct formation was observed, but starting material (*ca.* 80%) was recovered. When the above reactions were repeated, employing N,N,-dimethylformamide or dimethylsulphoxide as solvent, decomposition of starting material (adduct) occurred in each case, with no formation of diadduct.

9.11 Attempted selective reductions of adducts(399) and (401)

9.11.1 Attempts to selectively reduce the ester functionality of adducts(399) and (401) with lithium aluminium hydride

9.11.1.1 In tetrahydrofuran

To the grey suspension of lithium aluminium hydride (0.4g, large excess) in anhydrous, freshly distilled tetrahydrofuran (40 ml), the adduct (401) (0.2g) was added. The resulting brown suspension was heated under reflux for 6 h. After the addition of ethyl acetate (3 ml) and water (20 ml), the solvent (tetrahydrofuran) was removed under reduced pressure. The product was extracted from the aqueous suspension with ethylacetate. Removal of solvents under reduced pressure (0.1 mm.Hg.) afforded a dark yellow 'oily' solid (0.18g), which was found to be a crude mixture containing decomposition products (thin layer chromatography, and infrared and mass spectroscopy).

9.11.1.2 In diethyl ether

To the grey suspension of lithium aluminium hydride (0.3g, large excess) in anhydrous freshly distilled diethyl ether (30 ml), the adduct (401) (0.2g) was added. The resulting grey emulsion was stirred at 25^{o} for 12 h, then water (10 ml) was added dropwise. After the removal of diethyl ether under reduced pressure, the solids were isolated by filtration then washed several times with water. The product was extracted from the solids with dimethyl sulphoxide. Drying of the dimethyl sulphoxide extract with anhydrous magnesium sulphate, followed by removal of solvent (dimethyl sulphoxide) under reduced pressure (0.1 mm.Hg.) furnished a pale-yellow solid (0.17g), found to contain a mixture of products.

ν_{max} (KCl disc) 3,300; 2,920; 2,860; 1,715; 1,670; 1,630; 1,600; 1,500 cm^{-1}.

Mass Spec.:- 376; 362; 344 m/e.

9.11.2 Attempts to selectively reduce the carbonyl functionalities of adducts (399) and (401) with sodium borohydride

9.11.2.1 With sodium borohydride/ethanol

To an emulsion of the adduct(399) (0.10g) in ethanol (20 ml, 95%), sodium borohydride (0.5g, large excess) was added. The resulting mixture was stirred for 4 h at 25°. After the addition of water (10 ml) stirring was continued for a further 12 h at 25°. Removal of solvents (ethanol and water) under reduced pressure gave a white solid, which was washed several times with cold water. The white solid was found to be a mixture of starting material (399) and several decomposition products (thin layer chromatography and mass spectroscopy).

9.11.2.2 With sodium borohydride/methanol/ethanol

To a stirred suspension of the adduct(401) (0.10g) in a mixture of methanol (1 ml) and ethanol (3 ml), sodium borohydride (0.5g, large excess) was added portionwise over 10 minutes. The mixture was heated under reflux for 2 h (reaction followed by thin layer chromatography on silica, solvent J elution, until complete loss of starting material(401) observed).

Water (10 ml) was added to the grey emulsion giving an almost clear solution (pH = 10-11). Glacial acetic acid was added dropwise until effervescence ceased. The solution was then basified by the dropwise addition of aqueous sodium hydroxide solution (4M). The product was

extracted with dichloromethane, washed with water, dried (anhydrous magnesium sulphate) and finally, removal of solvent (dichloromethane) under reduced pressure gave a brown 'oily' solid containing three different products.

The three components of the mixture were separated by preparative thin layer chromatography on silica, solvent J elution:- Fraction A, R_f = 0.15

Fraction B, R_f = 0.35

Fraction C, R_f = 0.80

(Fraction A undergoes decomposition whilst standing for 24h. at 25°).

Data for Fraction C:-

$\nu_{max.}$ (neat film) 3,400 (broad);3,060;3,960; 1,630;1,420cm^{-1}

$^1H_{nmr}$ δ $(CD_3)_2.SO$ 7.9-8.1 (1H, m. aromatic proton);

6.9-7.7 (7H, m, aromatic protons);

6.5-6.8 (1H, m, aromatic proton);

6.1-6.4 (1H, m, olefinic proton);

3.8-4.6 (4H, m, aliphatic protons);

3.3-3.7 (5H, m, $-OCH_3$ and aliphatic protons);

3.1 (3H, s, $>N-CH_3$); 2.3-2.5 (2H,m, $-CH_2-$);

1.4-1.6 (2H, m, $-CH_2-$) ppm.

Mass spec.:- 374 (M^+); 359 m/e

9.11.2.3 With sodium borohydride/acetic acid

To a cooled (0°) suspension of the adduct (401) (0.2 g) in tetrahydrofuran (10 ml), sodium borohydride (1.0 g, large excess) was added. Acetic acid (6 ml) in tetrahydrofuran (10 ml) was then added dropwise to the stirred suspension at 0° over 0.5 h. The resulting mixture was heated (55°) under reflux

until complete loss of starting material (401) occurred (reaction followed by T.l.c. on silica) (ca. 6h). After the addition of acetic acid (10 ml) and water (20 ml), the product(s) was extracted with chloroform, washed with water, dried over anhydrous magnesium sulphate and finally, removal of solvent (chloroform) under reduced pressure afforded a pale-yellow solid (0.18 g). The solid was found to be a mixture of four products, which could not be separated satisfactorily by preparative T.l.c. or crystallization procedures.

$\nu_{max.}$ (KCl disc.) 3,350; 2,960; 1.710; 1,635; 1,600,1,500 cm^{-1}

9.11.3 Attempted selective reduction of one or more carbonyl functionalities of adducts (399) and (401) with diborane

General Procedure

To a suspension of the adduct (399) or (401) (0.2 g) in anhydrous diethylene glycol dimethyl ether (20 ml) under an atmosphere of nitrogen, diborane (B_2H_6: THF) (5 equivalents) was added at 0° over 0.25 h. The resulting grey emulsion was stirred at 25° for 12h. under nitrogen. After the dropwise addition of aqueous sodium hydroxide solution (5 ml., 5M) and hydrogen peroxide (5 ml., 50%) at 0°, the mixture was stirred at 25° for 18 h.

The product(s) was extracted with diethyl ether, washed with water (3x), dried with anhydrous magnesium sulphate and finally, removal of solvent (ether) under reduced pressure afforded a white or pale-yellow solid. The solid was found to consist of a mixture of 4-7 components by T.l.c. Although some reduced products were present, some degradation products of starting materials (399) or (401) were also present.

CHAPTER TEN

DIAZASTEROID INTERMEDIATES FROM 4-SUBSTITUTED QUINAZOLINES

10.1.1 4-Hydroxyquinazoline(415)

Anthranilic acid (68.5g, 0.5M) was heated with an excess of formamide (45g) for 3 h. at 120-130°. Filtration of the pale-yellow solid on a buchner funnel, followed by recrystallization from aqueous ethanol (95%) yielded colourless needles (72.1g, 98%), m.p. 215-216° (lit.[507] 215-217°).

ν_{max} (Nujol)	3,200(OH); 1,700(>C=O) cm^{-1}.
^1H nmr $\delta_{(CD_3)_2CO}$	8.35(1H,s,C_2-H); 8.12(1H,s,-OH); 7.5-8.25 (4H,m,aromatic protons) ppm.
Mass Spec.	146(M^+) m/e

10.1.2 2-Methyl-4-hydroxyquinazoline(416)[508]

Anthranilic acid (50g) and acetic anhydride (150 ml) were heated together under reflux for 1.5 h. The off-white solid, obtained by removal of the acetic acid and excess acetic anhydride, by distillation under reduced pressure, was washed with di-isopropyl ether. The intermediate(416A) (2-methyl,3,1,4-benzoxazone) (m.p. 114-116°), was allowed to dry in air.

ν_{max} (liquid paraffin)	1,740; 1,670; 1,630; 1,590; 1,570; 1,500; 1,280; 1,220 cm^{-1}.
^1H nmr $\delta_{(CD_3)_2SO}$	7.70-8.50(4H,m,aromatic protons); 2.39(3H,s,-CH_3) ppm.
Mass Spec.	161(M^+); 146 m/e.

3,1,4-Benzoxazone(416A) was crushed to a fine powder and then suspended in concentrated ammonia solution (0.880 S.G.). The yellow suspension was shaken for 24 h., after which, sodium hydroxide (10% aq. solution, 20 ml) was added. The mixture was heated on a water bath until bubbling ceased. The yellow suspension was dissolved completely by the addition of sodium hydroxide (10% solution, ca. 200 ml). The resulting brown solution was treated with decolourising charcoal and filtered whilst hot. Acidification of the yellow filtrate with glacial acetic acid, followed by cooling in an ice-bath furnished colourless crystals. The produce was isolated by filtration, washed with ice-water and dried in a vacuum oven (100°); m.p. 233-234°[508] (53g, 91%).

$\nu_{max(liquid\ paraffin)}$ 3,300; 1,640; 1,620; 1,590; 1,310; 1,130 cm^{-1}.

^1H nmr $\delta_{(CD_3)_2.SO}$ 7.60-8.15(4H,m,aromatic protons); 2.40(3H,s,-CH_3) ppm.

Mass Spec. 160(M^+); 145 m/e.

10.2.1 4-Chloroquinazoline(417)

10.2.1.1

4-Hydroxyquinazoline (15.0g) was stirred with freshly distilled thionyl chloride (60 ml). Phosphorus pentachloride (2.2g), N,N-dimethylformamide (2 ml), and benzene 20 ml) were added to the stirred suspension. The mixture was heated under reflux for 4.5 h. The resulting clear yellow solution was evaporated to dryness under reduced pressure to give a pale-yellow solid. The yellow solid

was extracted with chloroform (500 ml), washed with sodium bicarbonate (6.0g)-ice/water mixture, and finally washed with ice-cold water (3 x 100 ml portions). The solvent was removed under reduced pressure at 25° to yield a yellow solid, which recrystallised from petroleum ether (b.p. 40-60°) to give pale yellow crystals (13.5g, 80%), m.p. 97-98° (lit.[509] 98°).

ν_{max} liquid paraffin cm^{-1}	1,640(>C=N-); 1,590; 1,502; 1,012; 790.
^1H nmr δ_{CDCl_3} ppm	9.18(1H,s,C_2-H); 7.7-8.4(4H,m,aromatic protons).
Mass Spec.	164(M^+); 129 m/e.

10.2.1.2

4-Hydroxyquinazoline(8.0g), phosphorus pentachloride (15.0g) and phosphorus oxychloride (70 ml) were mixed together and heated under reflux for 2.5 h. at 115-118°. The phosphorus oxychloride was removed by distillation under reduced pressure. The residue was extracted with ether (3 x 200 ml portions). The combined ether extracts were basified with sodium bicarbonate (ca. 4g), washed with water and finally dried (anhydrous magnesium sulphate). Removal of the solvent under reduced pressure gave a pale-yellow solid (5.6g, 63%), m.p. 98° (lit.[507] 96.5-97.5°).
Analytical data similar to that for experiment 10.2.1.1.

10.2.2 2-Methyl,4-chloroquinazoline(418)

2-Methyl,4-hydroxyquinazoline (10g) in thionyl chloride (30 ml) and dimethylformamide (1 ml) was heated under reflux for 24 h. After removal of the thionyl chloride under reduced pressure, the

orange solid was extracted with dichloromethane (200 ml) and washed with an ice-cold aqueous solution of sodium bicarbonate (3g, 50 ml), followed by water (2 x 50 ml). The organic phase was dried with anhydrous magnesium sulphate, after which the solvent was removed under reduced pressure to yield a yellow solid (4.2g, 38%). Recrystallization from heptane afforded pale yellow crystals, m.p. 82-83° (lit.[510] 81.5-83°).

Mass Spec. 178(M^+), 143 m/e.

10.3 3,4-Dihydro-4-oxo-3-quinazolin-4'-yl-quinazoline(419)

When 4-chloroquinazoline(417) is heated to above 50°, treated with acid, or allowed to stand in the presence of 4-hydroxyquinazoline, the 'dimer'(419) results. Recrystallization from aqueous ethanol (50%) furnished pale yellow crystals, m.p. 233° (lit.[511] 232°).

ν_{max} (liquid paraffin) 1,685; 1,617; 1,320 cm^{-1}.

^1H nmr δ_{CDCl_3} 9.00(2H,s,$C_{2,2'}$-H's); 7.60-8.30(8H,m, aromatic protons) ppm.

Mass Spec. 274(M^+) m/e.

Elemental Analysis: $C_{16}H_{10}N_4O$ requires C,70.0%; H,3.7%; N,20.4%

found C,70.0%; H,3.7%; N,20.3%.

10.4 4-(α-Ethoxycarbonyl)methylquinazoline(420)

10.4.1

Redistilled and dried ethyl acetoacetate (8.2g) and sodium(1·44g) were stirred together at 25° in sodium-dried diethyl ether (200 ml) for 24 h. To the resulting milky suspension, freshly prepared and dried

4-chloroquinazoline (10.5g) was added. A further quantity of sodium-dried diethyl ether (200 ml) was added. The yellow mixture was refluxed for 36 h. After removal of the ether under reduced pressure, water (100 ml) was added to obtain a clear yellow solution of pH = 8-9. The solution was brought to pH = 6 by dropwise addition of hydrochloric acid (2M). The resulting white precipitate was removed by filtration and dried. Recrystallization from aqueous ethanol (50%) afforded pale yellow needles of product (420) (7.5g, 54%), m.p. 106° with softening at 82° (lit.[512] 105°). Two further recrystallizations from hexane (with decolourising charcoal) gave very fine colourless needles with m.p. 108° (lit.[512] 108-109°), in yields of < 30%.

ν_{max} (Nujol)	1,640(>C=N); 1,710(>C=O); 3,500(>N-H) cm^{-1}.
^1H nmr δ_{CDCl_3}	7.30-7.81(5H,m,aromatic protons); 5.42(1H,s,C_9-H); 4.15(2H,q,-CH_2-); 1.80(1H,s,>N-H); 1.3(3H,t,-CH_3) ppm.
Mass Spec.	216(M^+) m/e.

(See Appendix II for Carbon-13 spectral data.)

10.4.2

To a stirred solution of sodium ethoxide (1.4g sodium in 200 ml absolute ethanol), an ethanolic solution of 4-(α,α-diethoxycarbonyl)methylquinazoline(421) (4g in 20 ml) was added. After heating under reflux for 1.5 h., the mixture was poured into water (400 ml). The aqueous solution was acidified with hydrochloric acid (3M, ca. 20 ml) to pH = 5. The yellow precipitate thus produced was filtered, dried, and recrystallised from aqueous ethanol (50%) (using decolourizing charcoal) to yield pale yellow needles (2.6g, 86.6%), m.p. 106°.

Analytical data was found to be identical to that for product (420), Ex. 10.4.1.

10.5 4-(α,α-Diethoxycarbonyl)methylquinazoline(421)

To the white suspension of sodio-diethylmalonate, obtained by stirring sodium (1.75g) and redistilled diethylmalonate (12.5g) in sodium-dried diethyl ether (200 ml), freshly prepared and dried 4-chloroquinazoline (15g) was added. The resulting yellow mixture was heated under reflux for 48 h. The yellow solid was filtered off and added to water (100 ml), giving a solution of pH = 8.5. Neutralization of the mixture to pH = 7, by dropwise addition of sulphuric acid (2M) afforded a yellow precipitate (14g), which was isolated by filtration. The ethereal filtrate was shaken with sodium hydroxide (2M, 20 ml). Removal of the aqueous layer, followed by neutralization with sulphuric acid (2M) resulted in further precipitation of the product (2g). The crude precipitates of the product (16g) were combined. Recrystallization from hexane afforded pale-yellow crystals (14.5g, 55.1%) m.p. 86° (lit.[512] 85.5 - 86.5°) of the diester (421).

$\nu_{max_{(Nujol)}}$ 1,720(>C=O); 3,550(>N-H) cm^{-1}.

^1H nmr δ_{CDCl_3} 9.30(1H,s,C_2-H); 7.30-8.15(4H,m,aromatic protons); 5.54(1H,s,-CH<); 4.30(4H,q,-CH_2-); 1.31(3H,t,-CH_3); 1.29(3H,t,-CH_3) ppm.

Mass Spec. 288(M^+) m/e.

10.6 4-Ethoxyquinazoline(422)

To a suspension of 4-chloroquinazoline (8.5g) in diethyl ether (100 ml), an ethanolic solution of sodium ethoxide (1.2g sodium in 50 ml ethanol) was added. The yellow mixture was heated under reflux for 48 h. After neutralization of the mixture with hydrochloric acid (2M), the pale yellow precipitate which resulted, was isolated by filtration. Recrystallization from aqueous ethanol (95%) afforded colourless needles (8.4g, 93%), m.p. 45-47° (lit.[512] 47-49°) of 4-ethoxyquinazoline.

^{1}H nmr δ_{CDCl_3} 8.9(1H,s,C_2-H); 7.5-8.3(4H,m,aromatic protons); 4.6(2H,q,-CH_2-); 1.5(3H,t,-CH_3) ppm.

Mass Spec. 174(M^+), 159 m/e.

(See Appendix II for Carbon-13 spectral data)

10.7 4-Methylquinazoline(423)

10.7.1

The monoester(420) was boiled gently under reflux in an aqueous solution of sodium hydroxide (20%) for 3 h. After cooling the reaction mixture, the product was extracted from the yellow-green solution with diethyl ether. The ethereal extract was washed carefully with cold water, dried over anhydrous magnesium sulphate, and finally, the solvent removed under reduced pressure to afford a yellow oily solid, which on allowing to stand for 24 h., crystallized to give 4-methylquinazoline (46%), m.p. 35-37° (lit.[512] 33.5-36.5°).

^{1}H nmr δ_{CDCl_3} 9.1(1H,s,C_2-H); 7.3-7.9(4H,m,aromatic protons); 2.75(3H,s,-CH_3) ppm.

Mass Spec. 144(M^+); 129 m/e.

The picrate was prepared by adding a saturated solution of picric acid in ethanol (95%) to a solution of 4-methylquinazoline in absolute ethanol. On allowing the solution to cool at 0^{o}, pale green crystals resulted, which were recrystallized from aqueous ethanol (95%) to afford bright yellow platelets, m.p. 180-183^{o}.

Elemental Analysis: $C_{15}H_{11}N_5O_7$ requires C,48.3%;H,3.0%;N,18.8%
found C,48.1%;H,3.0%;N,18.7%

10.7.2

The diester(421) was heated under reflux in a methanolic solution of potassium hydroxide (10%) for 4 h. The resulting yellow solution was neutralised with hydrochloric acid (2M). After removal of the white precipitate by filtration, the solvent (methanol) was removed under reduced pressure to give a brown oil, which was extracted with diethyl ether. The ethereal extracts were combined, washed with ice-cold water (2x), dried over anhydrous magnesium sulphate, and finally, the solvent removed under reduced pressure to afford a yellow oily solid, which was crystallized from ether to give yellow platelets (67%), m.p. 34-37^{o} of 4-methylquinazoline. (Analytical data similar to that for Ex. 10.7.1.)

10.7.3

4-Methylquinazoline was also prepared *via* the Wittig reaction (Ex. 10.16.1).

10.8 4-(2-Dimethylaminoethyl)quinazoline hydrochloride(424)

Dimethylamine hydrochloride (0.6g) and formaldehyde (0.6 ml, 37% aqueous solution) were added to a solution of 4-methylquinazoline (1.0g) in absolute ethanol (20 ml). The resulting orange solution was stirred at 25° for 20 h. The solvents were removed under reduced pressure (0.1 mm Hg) at 35°, to afford a green oily solid (1.5g, 91%). A small amount was crystallized from an acetone/ethanol mixture to give yellow-green crystals, m.p. 121-125° (with softening at 80°). Although several attempts were made, it was not possible to satisfactorily recrystallize the product (424).

ν_{max} (liquid paraffin) 3,400; 1,650; 1,600; 1,560; 1,140 cm^{-1}.

^1H nmr $\delta_{(CD_3)_2SO}$ 9.0-9.3(1H,m,C_2-H); 7.7-8.8(4H,m,aromatic protons); 3.5-4.1(4H,m,$-CH_2-CH_2-$); 2.8-2.9 (6H,d, $\overset{\oplus}{N}(CH_3)_2$) ppm.

Mass Spec. 200 m/e.

Elemental Analysis: $C_{12}H_{16}N_3Cl$ requires C,60.7%;H,6.8%;N,17.7%; Cl,14.8%

found C,60.4%;H,6.7%;N,17.8%; Cl,15.2%

10.9 Michael reaction of 4-(2-dimethylaminoethyl)quinazoline(424) with 2-methylcyclopentane-1,3-dione

The Mannich base hydrochloride(424) (1.0g) and 2-methylcyclopentane-1,3-dione (0.5g) were added to t-butylalcohol (freshly distilled, 20 ml) containing potassium (0.2g). The grey suspension was heated under reflux for 24 h., under a steady stream of nitrogen. The resulting blue solution was carefully poured into water (40 ml), then extracted with chloroform (100 ml). The chloroform extract

was washed with water (2x10 ml), dried over anhydrous magnesium sulphate, and the solvent removed under reduced pressure to afford a brown oily solid. The product was then extracted with boiling petroleum ether (b.p. 60-80°). After removal of solvent under reduced pressure, an impure yellow solid was obtained in very low yield. Recrystallization from acetone, ethanol, etc. was not successful.

ν_{max} (Nujol) 1,710; 1,685 cm^{-1}.

Mass Spec. 268(M^+); 253 m/e.

10.10 Michael addition of methyl vinyl ketone to the diester(421)

To a solution of 4-(α,α-diethoxycarbonyl)methylquinazoline(421) (1.05g) in anhydrous ethanol (30 ml), freshly prepared sodium ethoxide [sodium (0.1g) in ethanol (1 ml)] was added at 0°, under an atmosphere of nitrogen. After stirring the pale yellow solution for 0.5 h. at 0°, methyl vinyl ketone (1.0g) was added and the resulting yellow-green solution stirred for a further 0.5 h, at 0°. The temperature was then raised to 25° and stirring continued under an atmosphere of nitrogen for ca. 24 h. (Reaction was allowed to proceed at 25° until complete loss of starting material was observed, by withdrawing small aliquots of the mother liquor and examining by thin layer chromatography.) After the addition of water (5 ml) to the reaction mixture, the solvents (ethanol/water) were removed under reduced pressure at 50°. The product was extracted into diethyl ether from the resulting dark yellow oil, washed with water, dried (magnesium sulphate), and finally the ether removed under reduced

pressure to afford a yellow 'oily' solid (0.28g). The product (427) could not be crystallized satisfactorily.

^{1}H nmr δ_{CDCl_3} 6.8-8.1 (5H,m,aromatic protons); 3.5-3.9(4H,q,2x-$C\underline{H}_2$-CH_3); 2.1-2.3(3H,$C\underline{H}_3$·CO); 1.5-1.9(4H,m,-$C\underline{H}_2$-$C\underline{H}_2$-); 1.0-1.4(6H,t,2x-$C\underline{H}_3$); 4.0-4.4(broad,water?); 2.3-3.0 (broad, solvent?) ppm.

Mass Spec. 358(M^+); 343; 298 m/e.

10.11 N-Methylation of 4-(α-ethoxycarbonyl)methylquinazoline(420)

Methyl iodide (10 ml, large excess) was added dropwise to a solution of the ester(420) (0.100g) in acetone (15 ml) at 0°. The resulting lemon-coloured solution was stirred at 25° for 48 h. (Reaction followed by Tlc until loss of starting material observed.) The excess methyl iodide was removed under reduced pressure. Diethyl ether (3 ml) was added to the cream suspension thus obtained, cooling of which at 0° for 2 h. afforded a pale-yellow precipitate. The precipitate was isolated by filtration, washed sparingly with cold water, then dried, to give the N-methylated product(428). Recrystallization from acetone/ethanol furnished almost colourless needles (0.092g, 87%), m.p. 168-170°.

ν_{max}(liquid paraffin) 1,660(>C=O); 1,635; 1,620; 1,510; 1,360; 1,320 cm^{-1}.

^{1}H nmr $\delta_{CDCl_3/(CD)_3\cdot SO}$ 8.98(1H,s,C_2-$\underline{H}$); 7.58-8.10(4H,m,aromatic protons); 6.10(1H,s,=$C\underline{H}$-); 4.3(2H,q,-$C\underline{H}_2$-); 3.95(3H,s,>N-$C\underline{H}_3$); 1.3(3H,t,-$C\underline{H}_3$) ppm.

Mass Spec. 230(M^+) m/e.

Elemental Analysis:- $C_{13}H_{14}N_2O_2$ requires C,67.8%; H,6.1%; N,12.2%

found C,67.9%; H,6.1%; N,12.3%.

10.12 N-Benzoylation of 4-(α-ethoxycarbonyl)methylquinazoline(420)

To a suspension of 4-(α-ethoxycarbonyl)methylquinazoline(420) (0.500g, 1 equivalent) in sodium-dried benzene (20 ml), benzoyl chloride (0.33g, 1 equivalent) and freshly distilled triethylamine (0.53g, 2 equivalents) were added at 0^{o}. The resulting yellow emulsion was stirred at 25^{o} for *ca.* 24 h. (Reaction followed by Tlc until loss of starting material(420) observed.) Solvent (benzene) and excess triethylamine were removed under reduced pressure $< 50^{o}$, to afford a yellow solid. The product was extracted into diethyl ether, washed with water, dried over anhydrous magnesium sulphate, and finally, removal of the solvent (diethyl ether) under reduced pressure gave a brown oily solid. The solid was washed with benzene, then crystallized from diethyl ether to furnish a yellow-green microcrystalline product(429), (0.42g, 57%), m.p. 100-105^{o}.

ν_{max}(liquid paraffin) 1,700(>C=O); 1,620 cm^{-1}.

^{1}H nmr δ_{CDCl_3} 8.1(1H,s,C_2-H); 7.3-7.8(9H,m,aromatic protons); 5.92(1H,s,=CH-); 4.2(2H,q,-CH_2-); 1.35(3H,t,-CH_3) ppm.

[also 3.2(q,-CH_2-) and 1.4(t,-CH_3) ppm. due to impurity - $(C_2H_5)_3\cdot\overset{\oplus}{N}\cdot HCl^{\ominus}$.]

Mass Spec. (338), 320(M^{+}) m/e.

Elemental Analysis:- $C_{19}H_{16}N_2O_3\cdot H_2O$ requires C,67.5%; H,5.3%: N,8.3%

found C,67.8%; H,5.4%; N,8.2%.

10.13 N-Acetylation of 4-ethoxyquinazoline(422)

To a solution of 4-ethoxyquinazoline(422)(0.500g, 1 equiv.) in sodium-dried benzene (20 ml), acetyl chloride (0.23g, 1 equiv.) in sodium-dried benzene (5 ml) was added dropwise at 0^{o} under an inert atmosphere of nitrogen. The resulting mixture was stirred for 72 h. at 25^{o}. (Complete loss of starting material(422) was not achieved, as observed by Tlc.) Reaction mixture was heated under reflux for a further 12 h., after which solvent (benzene) was removed under reduced pressure to afford a yellow-green impure solid (0.41g), m.p. 50-56°, containing the required product(430) and some starting material(422). Purification of product (430) by recrystallization from aqueous ethanol or diethyl ether was unsuccessful.

^{1}H nmr $\delta_{CDCl_3/(CD_3)_2.SO}$ 8.7(1H,s,C_2-H); 7.3-81(4H,m,aromatic protons); 4.5(2H,q,-CH_2-); 2.05(3H,s, -CO·CH_3); 1.4(3H,t,-CH_3) ppm.

Mass Spec. 217 (M^+); 174 m/e.

10.14 N-Benzoylation of 4-(α,α-diethoxycarbonyl)methylquinazoline(421)

To a suspension of the diester(421) (0.500g) in sodium-dried benzene (20 ml), benzoyl chloride (0.25g) in benzene (10 ml) and triethylamine (0.2g) were added dropwise at 0^{o} under an atmosphere of nitrogen. After stirring the mixture at 25^{o} for *ca.* 18 h. (until complete loss of starting material(421) was observed with Tlc), the white precipitate ($(C_2H_5)_3.\overset{\oplus}{N}.H\overset{\ominus}{Cl}$) which had resulted was removed by filtration. The yellow filtrate was carefully washed with water, dried over anhydrous magnesium sulphate and finally,

removal of the solvent (benzene) under reduced pressure afforded a pale-yellow solid, (0.52g), m.p. 76-79° which was found to be the required product (435) contaminated with impurities (benzoic acid and triethylamine hydrochloride).

ν_{max} (liquid paraffin)	1,730(>C=O); 1,710(>C=O); 1,680(>C=O) cm^{-1}.
^1H nmr δ_{CDCl_3}	8.5(1H,s,C_2-H); 7.4-8.2(9H,m,aromatic protons); 4.2-4.5(2H,q,-CH_2-); 3.9-4.2(2H, q,-CH_2-); 1.2-1.4(3H,t,-CH_3); 0.8-1.0(3H, t,-CH_3) ppm.
Mass Spec.	392(M^+), 226, 198 m/e.

10.15 Preparation of Starting Materials

10.15.1 Pyrrolidine enamine(437) of cyclopentanone

A mixture of freshly distilled cyclopentanone (8.4g, 1 equiv.) and pyrrolidine (14.2g, 2 equiv.) in sodium-dried benzene (100 ml) was boiled in a flask fitted with a Dean and Stark separator until the calculated amount of water was azeotropically removed (ca. 5 h). Removal of solvent from the resulting dark red solution under reduced pressure, followed by distillation under nitrogen, furnished a colourless liquid(437) (9.8g, 72% based on cyclopentanone), b.p. 40° at 1 mm Hg P.

^1H nmr δ_{neat}	3.95(1H,s,C_7-H); 2.85-3.15(4H,m,$C_{2,5}$-H's); 2.15-2.55(4H,m,$C_{8,10}$-H's); 1.50-2.00(6H,m, $C_{3,4,9}$-H's) ppm.
Mass Spec.	137(M^+) m/e.

10.15.2 2-Hydroxymethylenecyclopentanone(438)[513,514]

Above was prepared as described in literature,[513] in 16% yield, m.p. 74-76°.

ν_{max} KBr disc 3,700(-OH); 1,740(>C=O); 1,670(>C=O) cm^{-1}.

^1H nmr $\delta_{(CD_3)_2.SO}$ 5.10(1H,s,=CH-OH); 4.05(1H,broad,-OH); 1.8-3.0 (6H,m,$C_{3,4,5}$-H's) ppm.

Mass Spec. 112(M^+) m/e.

10.15.3 n-Butyllithium[515]

Prepared as described in literature,[515] and stored under nitrogen.

10.15.4 Triphenylmethylphosphonium iodide $[(C_6H_5)_3.\overset{\oplus}{P}.CH_3]I^{\ominus}$

Preparation of above similar to that described in literature for the bromide.[516]

(yield 82%, m.p. 167-169°)

Mass Spec. 277, 199 m/e.

10.16 Wittig reaction of 4-chloroquinazoline(417)

To a suspension of triphenylmethylphosphonium bromide (7.16g, 20 mM) in anhydrous 1,2-dimethoxyethane (distilled from lithium aluminium hydride)(20 ml), under nitrogen, n-butyllithium (1.28g, 20 mM) in hexane was added at -65°. After allowing the pale yellow emulsion to stir at -65° for 2 h., 4-chloroquinazoline (1.64, 10 mM) dissolved in anhydrous,1,2-dimethoxyethane (5 ml), was added dropwise. The resulting mixture was stirred at -65° for 3 h. then at 25° for 12 h. under an atmosphere of nitrogen.

The quinazoline ylid thus formed, was "worked-up" *in situ*, *via* three different procedures to obtain the various quinazoline derivatives:-

10.16.1 Hydrolysis of ylid to obtain 4-methylquinazoline(423)

After the addition of a solution of sodium carbonate (2.12g, 20 mM) in water (5 ml) to the ylid (10 mM), the mixture was heated under reflux for 2 h., cooled, then extracted with diethyl ether. The ether extract was washed with water, dried over anhydrous magnesium sulphate and finally, removal of solvent (diethyl ether) under reduced pressure gave a brown oil. Distillation of the crude 'oily' product under reduced pressure (0.1 mm Hg) afforded an analytically pure product (423), 4-methylquinazoline (0.93g, 65%), m.p. 36^{o}-37^{o}. [See Ex. 10.7 for analytical data.]

10.16.2 Reaction of ylid with acetone to obtain 4-(2-methyl-1-propenyl) quinazoline(439)

To the ylid (10 mM) under an atmosphere of nitrogen, freshly distilled anhydrous acetone* (2.3g, 40 mM) in 1,2-dimethoxyethane (10 ml) was added dropwise at 0^{o}. The resulting mixture was stirred for 24 h. at 25^{o} under an atmosphere of nitrogen. After removal of the solvent (1,2-dimethoxyethane) and excess reagent (acetone) under reduced pressure, the product was extracted with hot diethyl ether. The combined ether extracts were dried (anhydrous magnesium sulphate). Removal of solvent under reduced pressure afforded a brown solid, treatment of which with excess mercuric chloride in aqueous ethanol (25%) resulted in precipitation of a bright yellow mercuric chloride salt of the product. The salt was isolated by filtration, washed

carefully with aqueous ethanol and finally, the product was freed by treating the salt with hydrogen sulphide followed by sodium carbonate in aqueous ethanol (10%). The mixture was filtered through a 'Celite' bed to give a yellow filtrate, removal of solvents from which, under reduced pressure afforded† a pale yellow solid (0.61g) m.p. 48-52°. Attempts to purify product (439) by recrystallization from aqueous ethanol or acetone/ether were unsuccessful. Distillation under reduced pressure resulted in decomposition of product.

ν_{max} (KBr disc)	1,670; 1,620; 1,570; 1,495 cm^{-1}.
^1H nmr δ_{CDCl_3}	8.8(1H,s,C_2-H); 7.4-8.4(4H,m,aromatic protons); 6.2(1H,m,olefinic proton); 2.1(3H,m,-CH_3); 1.9(3H,s,-CH_3) ppm.
Mass Spec.	184(M^+) m/e.

10.16.3 Reaction of ylid with benzaldehyde to obtain 4-styrylquinazoline(440)

Procedure for Ex.10.16.2 was repeated, but freshly distilled, anhydrous benzaldehyde* (4.2g, 40 mM) in 1,2-dimethoxyethane (10 ml) was added in place of acetone* to the ylid.

Finally, a yellow solid was obtained, recrystallization of which from diethyl ether/ethanol afforded almost colourless crystals of product (440), (0.27g, 12%) m.p. 97-99° (lit.[518] 94-95°).

(Also see Ex. 10.19.2)

ν_{max} (liquid paraffin)	1,700; 1,635; 1,610; 1,540 cm^{-1}.
^1H nmr δ_{CDCl_3}	8.8(1H,s,C_2-H); 7.3-8.4(11H,m,9 aromatic protons and 2 olefinic protons) ppm.

Mass Spec. 232(M^+).

Elemental Analysis:- $C_{16}H_{12}N_2$ requires C,82.7; H,5.2; N,12.0%

found C,82.9; H,5.1; N,12.1%

10.17 Attempted reduction of 4-(α-ethoxycarbonyl)methylquinazoline(420) and 4-(α,α-diethoxycarbonyl)methylquinazoline(421)

10.17.1 With sodium borohydride($NaBH_4$)

To the monoester(420) (1.0g) or the diester(421) (1.0g) dissolved in aqueous ethanol (80%) (20 ml), an excess of $NaBH_4$ (2g) was added slowly at 0°. The resulting mixture was stirred at 25° and the reaction followed by UV spectroscopy until no further change was observed (ca. 6 h). Sodium hydroxide (5 ml, 5M) and hydrogen peroxide (5 ml, 50%) were carefully added to the reaction mixture at 0°. Stirring of the mixture was continued for a further 4 h. at 25° to effect decomposition of the borate complex. After the addition of sodium chloride (5g) to the yellow emulsion, the product was extracted with chloroform. The chloroform extract was washed with water, dried (anhydrous magnesium sulphate), and finally, removal of solvent (chloroform) under reduced pressure gave a yellow solid which was found to be a mixture of several products, none of which were the required products (441) or (442). Attempts to separate the components of the mixture by column (neutral alumina) chromatography led to decomposition of product(s). The crude mixtures were therefore discarded.

10.17.2 Catalysed hydrogenations

10.17.2.1 At atmospheric pressure

10.17.2.1.1

The monoester(420) (2.0g) dissolved in absolute ethanol (50 ml) was added to Adam's catalyst (PtO_2) (0.2g). After the removal of air, hydrogen was introduced into the reaction vessel connected to a gas burette (so that hydrogen uptake by starting material [420] could be quantitatively measured). The mixture was stirred at 25° for 72 h. Filtration of the black suspension through a 'Celite' bed (3 cm depth), followed by removal of solvent (ethanol) from the filtrate under reduced pressure, resulted in recovery of starting material(420). No reduction had occurred.

10.17.2.1.2

Ex. 10.17.2.1.1 was repeated, but palladium/charcoal (10%) (0.2g) was employed in place of platinum dioxide as catalyst. Again, starting material(420) was recovered; no reduction had taken place.

10.17.2.2 At a pressure of 6 atmospheres

10.17.2.2.1

A solution of the monoester(420) (1.0g) in absolute ethanol (30 ml) was added to Adam's catalyst (0.1g)* contained in a stainless steel flask. The flask was fitted to the hydrogenation apparatus. After removal of air, hydrogen was introduced into the flask and the pressure increased to 6 atmospheres. The flask was

then shaken at 25° for 24 h. at this pressure. The resulting black suspension was filtered through a 'Celite' bed (2.5 cm depth).† After removal of solvent (ethanol) from the yellow filtrate, the pale yellow solid (0.94g) obtained, was found to be a mixture of starting material(420) and the required product(441). Isolation and purification of the reduced product(441) by recrystallization from aqueous ethanol and ether/ethanol was unsuccessful.

ν_{max} (Nujol) 3,450(>N-H); 1,735(>C=O); 1,660 cm^{-1}.

Mass Spec. 218(M^+), 216(M^+) m/e.

10.17.2.2.2

A solution of the diester(421) (1.0g) in absolute ethanol (30 ml) was added to Adam's catalyst (0.15g) and the procedure* described for Ex. 10.17.2.2.1 followed.† After removal of solvent (ethanol) from the yellow filtrate, the solid obtained was recrystallized from ether/ethanol to afford almost colourless crystals of the reduced product(442), (0.89g, 88%), m.p. 59-62°.

ν_{max} (Nujol) 3,500(>NH); 1,725(>C=O); 1,665 cm^{-1}.

^{1}H nmr δ_{CDCl_3} 6.7-8.0(5H,m,aromatic protons); 4.6-4.9(1H, broad,>N<u>H</u>); 4.0-4.4(5H,m,2x-C<u>H</u>$_2$·CH$_3$ and -C<u>H</u>-N<); 3.5-3.8(1H,m,C<u>H</u><); 1.1-1.4(6H,t,2x-C<u>H</u>$_3$) ppm.

Mass Spec. 290(M^+), 288 m/e.

10.18 <u>4-Aminoquinazoline(443)</u>[520]

A mixture of 4-hydroxyquinazoline (2.92g, 20 mM) and phenyl phosphorodiamidate (4.30g, 25 mM) was heated to 230-240° in an oil

bath and the temperature maintained for 1.5 h. After cooling, the fused melt was crushed then added to n-butylamine (200 ml). The resulting suspension was heated under reflux for 3 h. The insoluble yellow/green residue was filtered off and discarded. Treatment of the brown filtrate with decolourizing charcoal, followed by removal of solvent (n-butylamine) under reduced pressure afforded a yellow oil, crystallization of which from n-butylamine furnished pale yellow needles of 4-aminoquinazoline(443), (1.98g, 68%), m.p. 267-269° (lit.[519] 267-268°).

$\nu_{max_{(Nujol)}}$	3,360(NH); 1,635(CN); 1,590; 1,560 cm^{-1}.
^1H nmr $\delta_{(CD_3)_2.SO}$	7.2-8.5(5H,m,aromatic protons); 4.6-6.0(2H, broad,-$\underline{NH}_2$) ppm.
Mass Spec.	145(M^+) m/e.

10.19 Condensation reactions with benzaldehyde

10.19.1 Reaction of 4-aminoquinazoline(443) with benzaldehyde

To a stirred suspension of 4-aminoquinazoline (0.73g, 5 mM) in sodium-dried, freshly distilled benzene (20 ml), freshly distilled benzaldehyde (2.1g, 20 mM) was added.* The mixture was boiled in a flask fitted with a Dean and Stark separator for 18 h. After removal of solvent (benzene) under reduced pressure, the product was extracted with chloroform. The chloroform extract was washed with a cold saturated aqueous solution of sodium bisulphite, then with water and finally, dried with anhydrous magnesium sulphate.† Removal of solvent (chloroform) under reduced pressure afforded a pale yellow solid, recrystallization of which from aqueous ethanol,

furnished an almost colourless microcrystalline product(444), (0.13g, 11%), m.p. 195-198°.

ν_{max} KCl disc 1,685; 1,640; 1,585 cm^{-1}.

^1H nmr δ_{CDCl_3} 8.52 (1H,s,aromatic proton); 7.2-8.2(10H, m,9 aromatic protons and 1 olefinic proton) ppm.

Mass Spec. 233(M^+) m/e.

Elemental Analysis:- $C_{15}H_{11}N_3$ requires C,77.3; H,4.7; N,18.0%

found C,77.6; H,4.6; N,17.9%.

10.19.2 Reaction of 4-methylquinazoline(423) with benzaldehyde

Freshly distilled benzaldehyde (2.1g, 20 mM) was added to a stirred emulsion of 4-methylquinazoline (0.72g, 5 mM) in sodium-dried benzene (20 ml), and the procedure described for 10.19.1 *repeated†.

After removal of solvent (chloroform) under reduced pressure, the yellow 'oily' solid obtained was crystallized from petroleum ether (b.p, 40-60°) to afford pale green crystals of product, 4-styrylquinazoline(440), (0.34g, 29%), m.p. 96-98° (lit.[518] 94-95°).

Mass Spec. 232(M^+) m/e.

(Analytical data similar to that given for Ex. 10.16.3.)

10.20 Attempted Diels-Alder reactions

General procedure

To a solution or suspension of the diene(440) (4-styrylquinazoline) or (444) (4-azastyrylquinazoline) (10 mM) in acetonitrile (30 ml), the dienophile (maleic anhydride or N-phenylmaleimide) (30 mM) was added. The reaction mixture was heated under reflux

for 24-72 h. (until loss of starting material [440] or [444] was observed by Tlc, elution solvent I). After removal of solvent (acetonitrile) under reduced pressure, the crude reaction mixture was examined by proton magnetic resonance spectroscopy and mass spectrometry.

10.20.1 Reaction of 4-styrylquinazoline with maleic anhydride

10.20.2 Reaction of 4-azastyrylquinazoline with N-phenylmaleimide

10.20.3 Reaction of 4-azastyrylquinazoline with maleic anhydride

Preliminary investigations suggest that complete loss of starting material (440) or (444) does not sometimes occur, even after a reaction time of 72 h. However some adduct formation may be occurring, together with several decomposition products.

Mass Spec. Reaction 10.20.3 360; 331(M^+); 197 m/e.

Reaction 10.20.2 422; 406(M^+) m/e.

Reaction 10.20.1 330(M^+); 252 m/e.

Analytical data - inconclusive.

10.21 Attempted reaction of 4-acetylenoquinazoline(451) with maleic anhydride to obtain adduct(452)

A solution of dried 4-chloroquinazoline (3.28g, 20 mM) in freshly distilled, anhydrous dimethylsulphoxide (10 ml) was added dropwise to a suspension of lithium acetylide ethylenediamine complex (2.76g, 30 mM) in dimethylsulphoxide (5 ml) at -30°, under an atmosphere of nitrogen. The resulting black suspension

was stirred at 0° for 2 h., then stirring continued at 25° for a further 0.5 h. under nitrogen. After the dropwise addition of water (10 ml), the product was extracted with chloroform. The yellow chloroform extract was dried (anhydrous magnesium sulphate).

ν_{max}(neat film) 3,300(C≡C); 1,655; 1,625; 1,600 cm^{-1}.

After reducing the solvent to low volume (under reduced pressure), maleic anhydride (3.92g, 40 mM) was added to the yellow solution. The resulting mixture was heated under reflux for 12 h. Removal of solvent under reduced pressure furnished a brown 'oily' solid, which was crystallized from petroleum ether (b.p. 40-60°) to give an impure product (0.87g), m.p. 66-87°. Further attempts to purify the product by recrystallization were unsuccessful.

ν_{max}(neat film) 2,500(=$\overset{\oplus}{N}$H?); 1,760(>C=O); 1,700(>C=O); 1,635(CN) cm^{-1}.

Mass Spec. 252; 247; 206 m/e.

PART III EXPERIMENTAL (CONTINUED)

C H A P T E R E L E V E N

AZASTEROIDS FROM BENZO[f]QUINAZOLINES

11.1 1,4-Dihydroxynaphthalene(455)

Crude 1,4-naphthaquinone (33g) was stirred with water (30 ml) and sodium hydrosulphite (67.5g). The suspension was diluted to 2.25 ℓ with hot water and then heated under reflux for 3 h. with addition of decolourizing charcoal. Filtration of the hot solution followed by cooling of the filtrate, furnished yellow crystals which were washed with sodium hydrosulphite (10% aqueous solution) and finally, dried in a vacuum desiccator in the absence of light. Recrystallization of product from aqueous ethanol (50%) afforded colourless crystals, (17g, 50%), m.p. 175-176° (lit.[521] 176°). (Tlc. on silica: solvent C elution; R_f = 0.61.)

ν_{max} (Nujol)	3,200(-OH); 1,625(>C=C<); 1,580 cm^{-1}.
^1H nmr $\delta_{(CD_3)_2CO}$	8.25(2H,s,2x-O<u>H</u>)(2H,q,aromatic protons); 7.45(2H,q,aromatic protons); 6.79(2H,q, aromatic protons) ppm.
Mass Spec.	160(M^+) m/e.

11.2 1,4-Dimethoxynaphthalene(456)

Dimethylsulphate (15 ml) was added in methanol (15 ml) to a solution of 1,4-dihydroxynaphthalene (6g) in methanol (45 ml) under nitrogen. Potassium hydroxide (18g) in water (45 ml) was then added dropwise over 1 h., under an atmosphere of nitrogen. The mixture containing colourless crystals was allowed to stand for 24 h. The crystalline solid was isolated by filtration, washed with aqueous methanol (30%), then recrystallized from

methanol to furnish colourless needles (6.5g, 95%), m.p. 86-87° (lit.[522] 86°). (Tlc on silica: solvent A elution, R_f = 0.81).

$\nu_{max(Nujol)}$ 1,625; 1,580 cm^{-1}.

^1H nmr $\delta_{(CD_3)_2\cdot CO}$ 8.18(2H,q,aromatic protons); 7.50(2H,q, aromatic protons); 6.80(2H,s,aromatic protons); 3.95(6H,s,2x-$C\underline{H}_3$) ppm.

Mass Spec. 188(M^+) m/e.

11.3 2-Chloromethyl-1,4-dimethoxynaphthalene(457)

1,4-Dimethoxynaphthalene was dissolved in a warm solution of monochloromethylether (6.6 ml) in glacial acetic acid (16.6 ml). After stirring the solution at 25° for 20 h., water (10 ml) was added and the product extracted with benzene. The benzene extract was washed with sodium carbonate solution (10%,aqueous, 3x20 ml), then with water (2x40 ml) followed by saturated sodium chloride solution (1x). After drying (anhydrous magnesium sulphate), solvent (benzene) was removed under reduced pressure and the brown residue distilled under reduced pressure. The yellow crystalline distillate, recrystallized from petroleum ether (b.p. 40-60°) furnished pale-yellow crystals (4.2g, 56%), m.p. 63-64° (lit.[523] 62-63°). (Tlc on silica: solvent A elution, R_f = 0.78)

$\nu_{max(Nujol)}$ 1,600(>C=C<) cm^{-1}.

^1H nmr $\delta_{(CD_3)_2\cdot CO}$ 8.15(2H,q,aromatic protons); 7.55(2H,q,aromatic protons); 6.91(1H,s,aromatic proton); 4.89(2H,s, s,-$C\underline{H}_2$·Cl); 3.95(6H,s,2x-$C\underline{H}_3$) ppm.

Mass Spec. 237(M^+) m/e.

11.4 1,4-Dimethoxy-2-naphthaldehyde(458)

To a solution of hexamine (5.5g) in chloroform (35 ml), 2-chloromethyl-1,4-dimethoxynaphthalene (7.5g) was added. The mixture was heated under reflux on a steam bath for 4 h. during which time a precipitate separated out. The reflux condenser was replaced by a condenser set for distillation and heating continued until solvent (17.5 ml) had distilled over. After the addition of acetone (17.5 ml), the mixture was cooled in an ice-bath. The precipitate was isolated by filtration, then dried in air to yield an iminium salt, m.p. 193°.

^{1}H nmr δ_{CDCl_3} 8.25(1H,q,-C<u>H</u>-N≤); 7.9(1H,q,aromatic proton); 7.60(2H,q,aromatic protons); 7.40(1H,s,aromatic proton); 7.28(1H,s,aromatic proton); 4.72(6H, s,2x-C<u>H</u>$_3$); 4.09(3H,s,-O.C<u>H</u>$_3$); 3.98(3H,s,-O.C<u>H</u>$_3$) ppm.

The salt was heated under reflux for 1 h. with acetic acid (50 ml, 50% aqueous solution). Water (50 ml) and concentrated hydrochloric acid (12.5 ml) were added, then boiling continued for a further 0.2 h. Cooling of mixture in an ice-bath furnished pale-yellow crystals of the aldehyde (4.2g, 61%), m.p. 117-118°. Recrystallization from aqueous ethanol (30%) gave almost colourless needles, m.p. 117° (lit.[524] 117°).[526]

(Tlc on silica: solvent A elution, R_f = 0.62)

$\nu_{max(Nujol)}$ 1,680(>C=O); 1,590 cm^{-1}.

^{1}H nmr δ_{CDCl_3} 10.80(1H,s,-C<u>H</u>O); 8.25(2H,q,aromatic protons); 7.60(2H,q,aromatic protons); 7.15(1H,s,aromatic proton); 4.15(3H,s,-OC<u>H</u>$_3$); 4.05(3H,s,-OC<u>H</u>$_3$) ppm.

Mass Spec. 216(M^+) m/e.

Elemental Analysis:- $C_{13}H_{12}O_3$ requires C,72.2%; H,5.5%

found C,72.3%; H,5.5%.

11.5 1-Hydroxy,4-methoxy,2-naphthaldehyde(459)

1,4-Dimethoxy-2-naphthaldehyde (5.7g) in anhydrous dichloromethane (20 ml), and boron trichloride (114 ml, 5 equivalents) in dichloromethane, were mixed at -70° and the flask was stoppered. The intense red coloured solution was stirred at 25° for 2.5 h. (Reaction was followed by Tlc until loss of starting material(458) was observed.) Water (100 ml) was added and stirring continued for a further 12 h. at 25°. The product was extracted with dichloromethane, washed with water (2x20 ml), dried with anhydrous magnesium sulphate, and finally, removal of solvent under reduced pressure furnished pale-green crystals of 1-hydroxy,4-methoxy, 2-naphthaldehyde (5.1g, 96%), m.p. 85-86°. The product was recrystallized from aqueous ethanol. (Tlc on silica: solvent A elution, R_f = 0.58.)

$\nu_{max(Nujol)}$ 3,400(-OH); 1,650(>C=O) cm^{-1}.

^1H nmr δ_{CDCl_3} 10.98(1H,s,-CHO); 9.88(1H,s,-OH); 8.40 (1H,d,aromatic proton); 8.20(2H,d,aromatic protons); 7.65(1H,q,aromatic proton); 6.71 (1H,S,aromatic proton);3.98(3H,s,-OCH_3) ppm.

Mass Spec. 202(M^+) m/e.

Elemental Analysis:- $C_{12}H_{10}O_3$ requires C,71.3%; H,5.0%

found C,71.1%; H,4.9%.

(See Appendix II for Carbon-13 spectral data).

11.6 1,4-Dihydroxy-2-naphthaldehyde(460)

1,4-Dimethoxy-2-naphthaldehyde (3.8g) in anhydrous dichloromethane (10 ml) was added to a solution of boron trichloride in dichloromethane (76 ml, 5 equivalents) at -70°, and the flask was stoppered. The intense red coloured solution was stirred at 25° for 6 h. Water (60 ml) was added to the mixture, and stirring continued for 24 h. The product was extracted with dichloromethane, dried with anhydrous magnesium sulphate and finally, removal of solvent under reduced pressure furnished the required product, 1,4-dihydroxy-2-naphthaldehyde (3.2g, 97%), m.p. 190-192° (lit.[525] 190°). (Tlc on silica: solvent A elution, R_f = 0.34)

Recrystallization of product (460) from aqueous ethanol (40%) gave yellow needles, m.p. 190-191°.

ν_{max} (Nujol) 3,350 (-OH); 1,670(>C=O) cm^{-1}.

^1H nmr δ_{CDCl_3} 12.4(1H,s,-OH); 9.8(1H,s,-OH); 10.8(1H,s, -CHO); 8.3(2H,q,aromatic protons); 7.7(2H,q, aromatic protons); 7.0(1H,s,aromatic proton) ppm.

Mass Spec. 188(M^+); 160 m/e.

Elemental Analysis:- $C_{11}H_8O_3$ requires C,70.2%; H,4.3%

found C,69.6%; H,4.5%

11.7 3-Aminobenzo[f]quinazoline(463)

A mixture of 2-hydroxy-1-naphthaldehyde (6.88g, 40 mM) and guanidine carbonate (10.8g, 60 mM) in n-octanol (20 ml) was heated under reflux for 4 h. at 160° (oil-bath), under an atmosphere of nitrogen. Benzene (100 ml) was added to the cooled mixture and stirring continued for 3 h. The dark red solid was isolated by

filtration, washed several times with cold water and then carefully with dichloromethane. Crystallization of the crude product from n-butanol (with decolourizing charcoal), followed by drying in a oven (110°, 0.05 mm Hg P) afforded pale yellow crystals of 3-aminobenzo[f]quinazoline(463) (1.94g, 25%), m.p. 257-259° (lit.[527] 258-259.5°).

ν_{max} (KCl disc)	3,420(>NH); 3,350(>NH); 3,100; 1,660; 1,590; 1,480; 1,330 cm^{-1}
^1H nmr $\delta_{(CD_3)_2SO}$	9.75(1H,s,C_1-aromatic proton); 8.60-8.80(1H,d, aromatic proton); 7.80-8.20(2H,m,aromatic protons); 7.40-7.80(3H,m,aromatic protons); 7.00(2H,broad,NH_2) ppm.
Mass Spec.	195(M^+); 179; 168 m/e.
Elemental Analysis:-	$C_{12}H_9N_3$ requires C,73.8%; H,4.6%; N,21.5%
	found C,74.2%; H,4.8%; N,21.8%.

11.8 Reaction of 1-hydroxy,4-methoxy,2-naphthaldehyde(459) with guanidine carbonate

Guanidine carbonate (1.08g, 6 mM) was added to a solution of 1-hydroxy,4-methoxy,2-naphthaldehyde(449) (0.61g, 3 mM) in n-octanol (10 ml), under an atmosphere of dry nitrogen. The mixture was heated under reflux at 150-160° (oil-bath) for 2 h. under nitrogen. After cooling the red emulsion to 25°, benzene (10 ml) was added, and stirring continued for 2 h. The yellow solid was isolated by filtration, washed several times with cold water, recrystallized from ethanol, then dried in a vacuum (0.1 mm Hg P) oven at 100° to furnish a yellow-green product(461), (0.13g, 19%), m.p. 293-296°.

^{1}H nmr $\delta_{(CD_3)_2 \cdot SO}$	8.8-9.0(1H,m,C_4-aromatic proton); 7.2-8.4 (5H,m,aromatic protons); 6.7(2H,broad,-N$\underline{H}_2$); 4.0(3H,s,-OC$\underline{H}_3$) ppm.
Mass Spec.	225(M^+) m/e.

11.9 3-Hydroxybenzo[f]quinazoline (466) from 3-aminobenzo[f]quinazoline via the diazonium intermediate

To a cooled (0°) mixture of 3-aminobenzo[f]quinazoline (0.20g) and hydrochloric acid (5M, 10 ml), sodium nitrite (1.0g, large excess) was added portionwise. The resulting cold emulsion was added dropwise to an aqueous solution of sulphuric acid (5M, 20 ml). After allowing to boil under reflux for 2 h., the mixture was basified with aqueous sodium hydroxide solution and then boiled vigorously for 0.5 h. without a reflux condenser in order to expel any volatile impurities. The white suspension was then neutralized by the dropwise addition of hydrochloric acid (2M). The product was isolated by filtration, washed several times with cold water, then recrystallization from dilute acetic acid (50%) furnished 3-hydroxybenzo[f]quinazoline(466) (0.15g, 75%), m.p. 328-331° (lit.[527] 330-332°).

$\nu_{max(Nujol)}$	3,500; 3,400; 1,680; 1,655; 1,630 cm^{-1}.
^{1}H nmr $\delta_{(CD_3)_2 \cdot SO}$	10.05(1H,s,-O$\underline{H}$); 9.85(1H,s,C_1-aromatic proton); 8.7(1H,d,aromatic proton); 7.4-8.3(5H,m, aromatic protons) ppm.
Mass Spec.	196(M^+) m/e.

11.10 N-Acetylation of 3-aminobenzo[f]quinazoline

To a suspension of 3-aminobenzo[f]quinazoline (0.20g, 1 mM) in sodium-dried toluene (20 ml), acetyl chloride (0.24g, 3 mM) in toluene (5 ml) was added, under an atmosphere of nitrogen. After the dropwise addition of triethylamine (0.3g, 3 mM) in toluene (5 ml) at 0^{o} under nitrogen, the resulting mixture was stirred at 25^{o} for 6 h. then heated under reflux for 3 h. (Reaction followed by Tlc on silica, solvent H elution; until complete loss of starting material [463] observed.) After removal of solvent (toluene) under reduced pressure, the product was extracted with diethyl ether, washed with water, dried (anhydrous magnesium sulphate) and finally, removal of solvent (diethyl ether) under reduced pressure furnished a yellow 'oily' solid. Crystallization from ether/ethanol afforded a pale-yellow microcrystalline solid (467), (0.11g, 45%), m.p. 210-214^{o}.

ν_{max} (KCl disc) 3,300(-NH); 1,650 (>C=O); 1,570; 1,520 cm^{-1}.

^{1}H nmr $\delta_{(CD_3)_2 \cdot SO}$ 9.80(1H,s,C_1-aromatic proton); 8.60-8.80 (1H,d,aromatic proton); 7.40-8.40(5H,m, aromatic protons); 6.93(1H,s,-NH); 2.35(3H, s,-CH_3) ppm.

Mass Spec. 237(M^{+}), 222 m/e.

Elemental Analysis:- $C_{14}H_{11}N_3O$ requires C,70.9%;H,4.6%; N,17.7%
found C,71.3%;H,4.7%; N,17.6%

11.11 N-Chloroacetylation of 3-aminobenzo[f]quinazoline(463) followed by cyclization of intermediate(468)

To a suspension of 3-aminobenzo[f]quinazoline (0.39g, 2 mM) in sodium-dried toluene (30 ml), freshly distilled, anhydrous

pyridine (0.32g, 4 mM) in toluene (5 ml) was added, under an atmosphere of nitrogen at 0^{o}. Chloroacetyl chloride (0.9g, 8 mM) was then added with a µl syringe over 10 minutes at 0^{o}. The reaction mixture was stirred at 0^{o} under nitrogen for 10 minutes, then stirring was continued for 2 h. at 25^{o}. After heating the yellow suspension under reflux for 6 h. the product was isolated by filtration, washed several times with cold water and finally, dried in a vacuum oven (0.1 mm Hg P) at 100^{o} to afford a yellow microcrystalline product(469) (0.23g, 43%), m.p. 283-285^{o} (with darkening at 170^{o}).

ν_{max}(liquid paraffin)	3,200(-NH); 1,660(>C=O) cm^{-1}.
^{1}H nmr $\delta_{CF_3 \cdot CO_2H}$	10.38(1H,s,C_1-aromatic proton); 8.60-8.95 (2H,m,aromatic protons); 7.95-8.35(5H,m, 4 aromatic protons and -NH); 4.60(2H,s,-CH_2) ppm.
Mass Spec.	271; 236(M^+); 221; 195 m/e.
Elemental Analysis:-	$C_{14}H_{10}N_3OCl$ requires C,62.0%;H,3.7%;N,15.5%; Cl,12.9%.
	found C,62.2%;H,3.6%;N,15.6%

APPENDIX I

Glossary

Ac	Acetyl
Bz	Benzyl
DDQ	2,3-Dichloro-4,5-dicyanobenzoquinone
DME	Dimethoxyethane
DMF	N,N-Dimethylformamide
DMSO	Dimethyl sulphoxide
DNP	Dinitrophenylhydrazone
EDTA	Ethylenediaminetetraacetic acid
Et	Ethyl
i-Bu	Isobutyl
IPA	Isopropenyl acetate
i-Pr	Isopropyl
LAH	Lithium aluminium hydride
MCPBA	m-Chloroperoxybenzoic acid
Me	Methyl
Ms	Methanesulphonyl
MVK	Methyl vinyl ketone
NBA	N-Bromoacetamide
NBS	N-Bromosuccinimide
n-Bu	n-Butyl
Ph	Phenyl
PPA	Polyphosphoric acid
Py	Pyridine
t-Bu	tert-Butyl
THF	Tetrahydrofuran
THP	Tetrahydropyranyl
Ts	p-Toluenesulphonyl

Purification/Drying of Solvents and Reagents

Acetone	- dried with anhydrous calcium sulphate or potassium carbonate
Benzene	- dried with sodium wire, then distilled. Stored over Linde 4X molecular sieve.
Dichloromethane	- dried with calcium chloride. Distilled from phosphorus pentoxide, then passed down an alumina column.
Diethyl ether	- dried with sodium wire, then distilled from lithium aluminium hydride.
1,2-Dimethoxyethane	- dried with sodium, then distilled from lithium aluminium hydride.
N,N-Dimethyl formamide	- dried with anhydrous magnesium sulphate, then distilled under reduced pressure.
Dimethylsulphoxide	- dried with calcium hydride, then distilled from calcium hydride. Stored over Linde 4A molecular sieve.
Ethanol (analar)	- dried with anhydrous calcium sulphate, then distilled. Stored over Linde 4A molecular sieve.
Methanol (analar)	- see procedure for Ethanol.
N-Methylformamide	- dried with molecular sieve, then distilled under reduced pressure through a column packed with glass helices.
Pyridine	- dried with potassium hydroxide, then distilled from potassium hydroxide. Stored over Linde 4A molecular sieve.
Tetrahydrofuran	- dried over calcium hydride, then distilled from lithium aluminium hydride after heating under reflux for 3h. Stored under nitrogen

in the absence of light.

Thionyl chloride - dried for 36h. with linseed oil, then distilled.

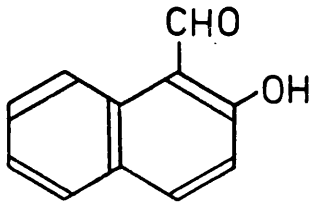
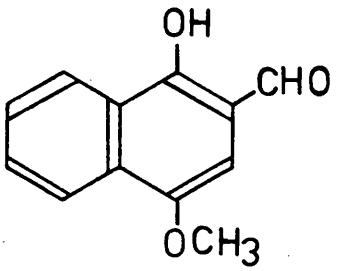
Toluene - dried with sodium wire, then distilled.

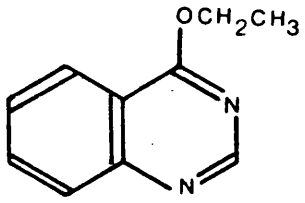
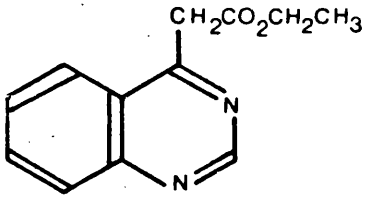
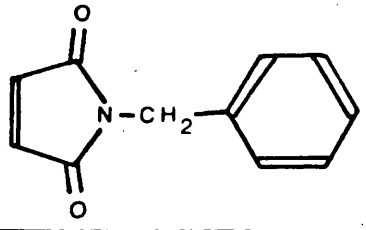
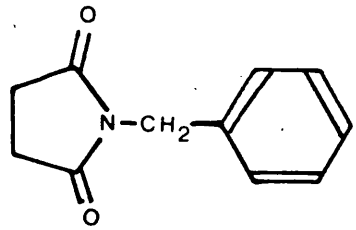
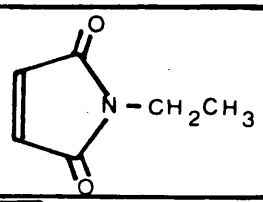
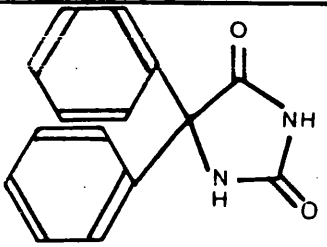
Triethylamine - dried, then distilled from potassium hydroxide, stored over molecular sieve,

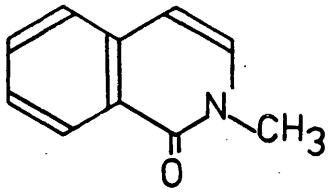
APPENDIX II

Although Carbon-13 nuclear magnetic resonance (^{13}C-nmr) spectroscopy is an invaluable technique for the study of organic compounds , it was not of significant value in this project, since many of the compounds concerned were large, complex structures. Also, in several cases, poor solubility of the nitrogen-containing steroidal molecules in the usual solvents, hindered any attempts to record the spectra. The few ^{13}C-nmr spectra that were recorded, were found to be ambiguous and extremely difficult to interpret as standard reference data to these compounds was not available (see Plate 6).

^{13}C-nmr spectra were obtained for the less-complex intermediates involved in this project, the data for some of which are given below:-

Intermediate	Carbon-13 nmr (δppm from TMS standard)
	δ_{CDCl_3} 192.97(C-11,d); 164.70(s),132.73(s), 127.64(s), 124.33(s),(C-1,C-2,C-9,C-10); 138.80(d), 129.31(d), 128.88(d),118 .97(d), 118.48(d), 111.17(d), (C-3,C-4,C-5,C-6, C-7, C-8) ppm.
	δ_{CDCl_3} 195.68(C-12,d); 156.51(C-1 ,s); 148.44(C-4,s); 130.24(s), 130.02(s), (C-9,C-10); 126.61(C-8,d); 124.17(C-6, C-7,d); 122.11 (C-5,d); 113.17(C-2,s); 101.79(C-3,d); 55.53(C-11,q) ppm

Intermediate	Carbon-13 nmr (δppm from TMS standard
	δ_{CDCl_3} 166.70(C-4,s); 154.56(C-2,d); 151.20(s), 116.80(s),(C-9, C-10); 133.27(C-7,d); 127.85(C-6,d); 126.77(d), 123.52(d), (C-5,C-8); 63.00 (C-11,t); 14.35 (C-12,q) ppm
	δ_{CDCl_3} 170.70(C-12,s); 154.61(C-2,d); 148.82(s), 144.60(s), (C-9,C-4); 142.53(d), 132.84(d), 128.07(d), 124.98(d), (C-5,C-6,C-7,C-8); 126.99 (C-10, s); 79.47 (C-11,t); 59.48(C-13,t); 14.52(C-14,q) ppm
	δ_{CDCl_3} 170.32(C-2,C-5,s); 136.30(C-7,s); 134.14 (C-3,C-4,d); 127.80-128.66 (C-8,C-9, C-10,C-11,C-12,m); 41.39 (C-6,t) ppm
	δ_{CDCl_3} 176.72(C-2,C-5,s); 135.98 (C-7,s); 127.91-128.88(C-8,C-9,C-10,C-11,C-12, m); 42.36 (C-6,t); 28.22(C-3,C-4,t) ppm
	δ_{CDCl_3} 170.60 (C-2,C-5,s); 134.20(C-3, C-4,d); 32.72 (C-6,t); 13.81(C-7,q) ppm
	$\delta_{(CD_3)_2.SO}$ 174.88(C-2,s); 156.13(C-4,s); 139.82(C-6,C-6',s); 126.55-128.45 (10 aromatic carbons, m); 70.37 (C-5,s) ppm

Intermediate	Carbon-13 nmr (δppm from TMS standard)
	δ_{CDCl_3} 198.54(C-1,s); 162.47(C-9,s); 137.22(C-10,s); 126.06-132.52(m), 125.90(d), (C-3,C-4,C-5,C-6, C-7, C-8); 36.73 (C-11, q) ppm

APPENDIX III

A Procedure for Biological Evaluation of Potentially Active Compounds.

Selection Procedure for Psychotropic Compounds*

Phase O: Toxicity-lethality study

mice : 100 and 320 mg./Kg.

rats: 46 mg./Kg.

Phase I: Spontaneous locomotor activity (mice).

Apomorphine-induced climbing (mice).

Muricidal behaviour (rats).

Ambulation-exploration (rats).

After Phase 1 testing the compound can be categorised in one of the five following possible "profiles":

A. General CNS depressant profile.

Activity in all tests is similarly decreased, even if compound is retested at lower doses.

B. "Neuroleptic" profile.

Apomorphine-induced climbing is inhibited at dose-levels not interfering with spontaneous locomotor behaviour.

C. "Antidepressant" profile.

Muricidal behaviour is depressed at dose-levels lower than those affecting spontaneous motor and exploratory behaviour.

D. "Anxiolytic" profile.

Spontaneous motor behaviour of mice is depressed whereas that of rats is increased. No further effects.

E. Unknown.

The compound either has no effects(E1), or has a profile not falling into one of the four classes mentioned above (E2).

Phase 2: (A): The compound is tested in the "sleeping test" (rats).

(B): 1. Dopamine turnover in selected rat-brain areas.

2. Motor coordination

3. Central anticholinergic properties (yawning test in rats).

4. Duration of action (time-response curve).

5. Ambulation-exploration (rats).

(C): 1. Shuttle box performance (rats).

2. Swimming test (rats or mice).

3. Uptake of noradrenaline and 5-hydroxytryptamine into rat synaptosomes.

4. Uptake of 5-hydroxytryptamine in human (preferably also depressed patient) platelets.

5. MAO inhibition.

6. Anti-appetite.

(D): 1. Anxiety test (rats).

2. Isolation-induced aggression (mice).

3. Stairway-test (rats).

4. GSP conflict test.

(E1): 1. High dose in shuttle box performance (to see whether compound is affecting CNS). If this is positive:-

at lower doses: 2. Appetite suppression (rats).

3. Sleeping test (rats).

4. Shuttle box acquisition (rats).

(E2): All phase 2 tests available.

Phase 3: Completion of the following list:-

1. Cardiovascular tests:-

- anaesthetized cats.

- conscious rabbits.

2. Ulcerogenicity.

3. Peripheral and central anticholinergic activity test:-

yawning test (rats).

skin resistance test (mice).

4. Motor coordination (rat rotarod).

5. Combined CNS-screen.

6. Peripheral profile.

Phase 4: 1. Haematological profile.

2. Endocrine profile.

3. Brain excitability tests.

4. Alcohol interaction.

5. All relevant tests from the following list:-

Reserpine tests.

5-HTP/tryptamine titration.

Emotional reactivity.

Isolation aggression of mice.

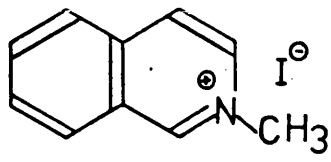
Pentetrazole titration.

Morphine interaction.

Appetite follow-up tests.

*The above details are as obtained from ORGANON LABORATORIES.

APPENDIX IV



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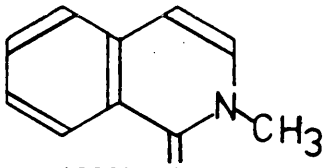

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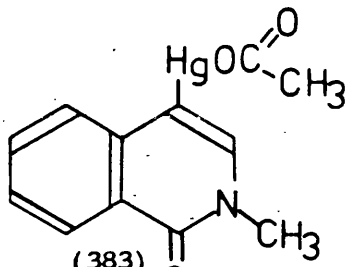

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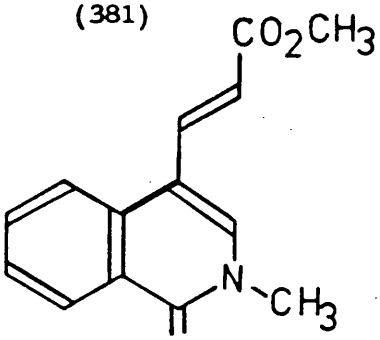

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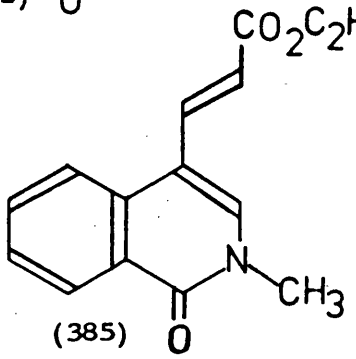

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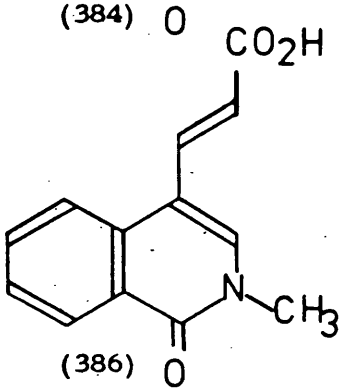

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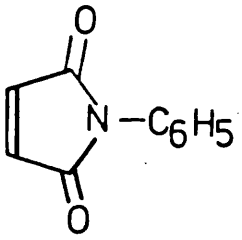

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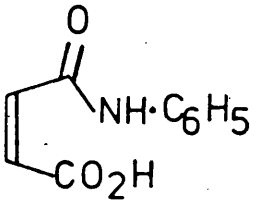

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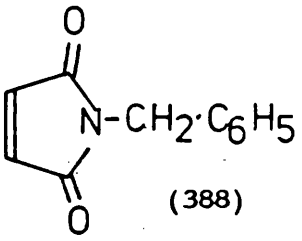

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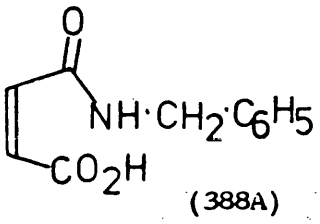

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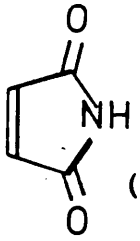

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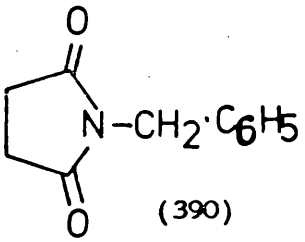

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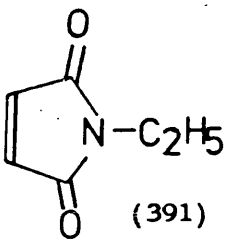

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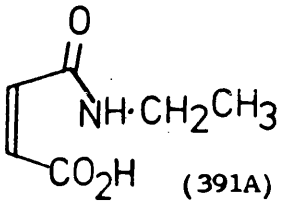

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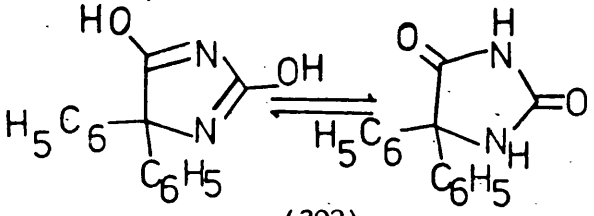

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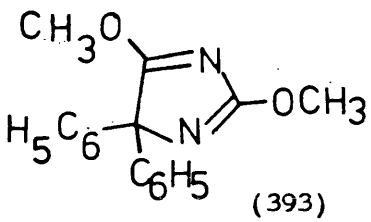

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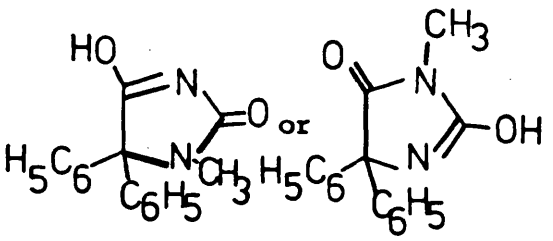

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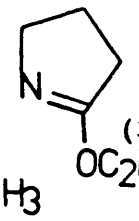

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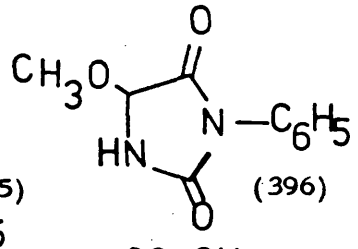

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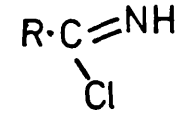
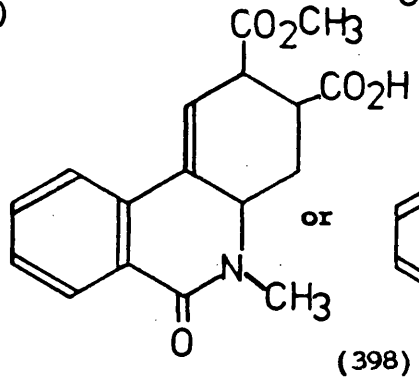


R = CH_3 ; C_6H_5

(397)



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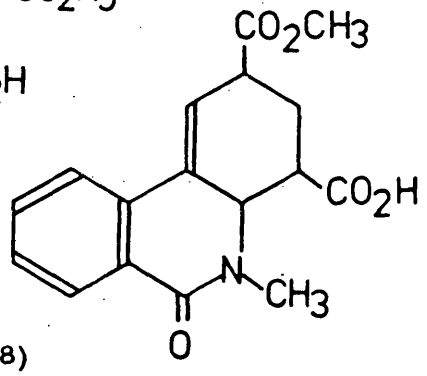

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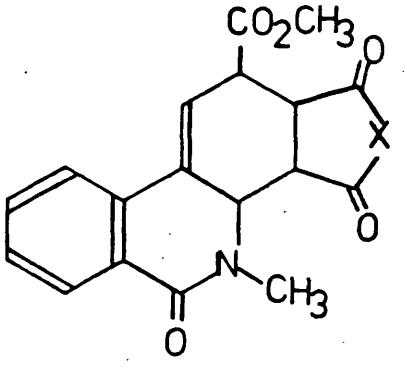
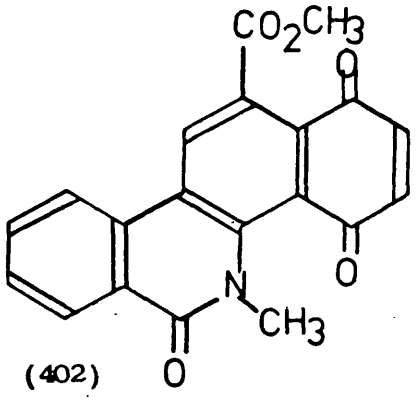


(399) X = $\geq O$

(400) X = $\geq CH_2$

(401) X = $\geq N-C_6H_5$



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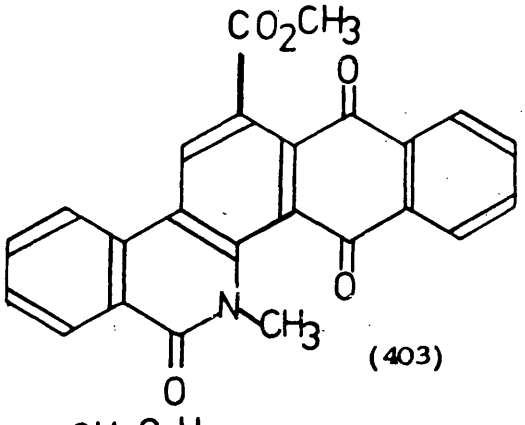

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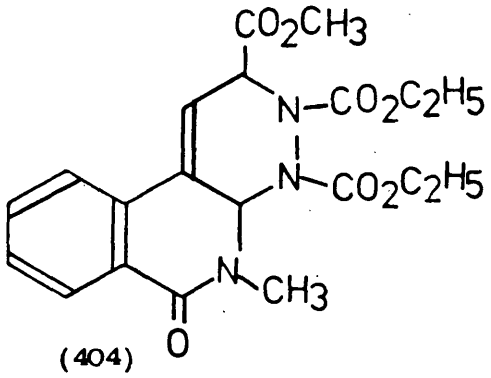

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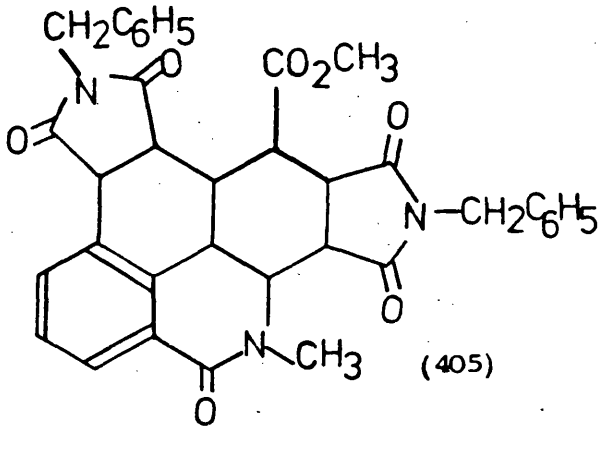

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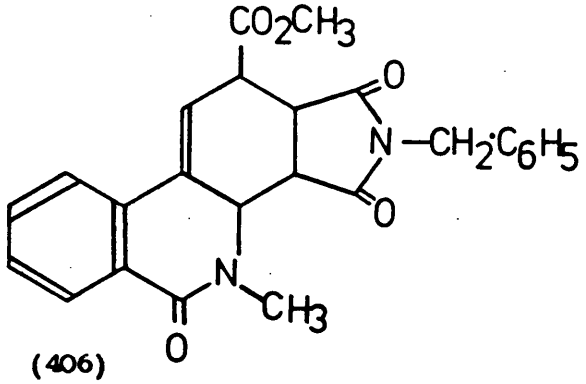

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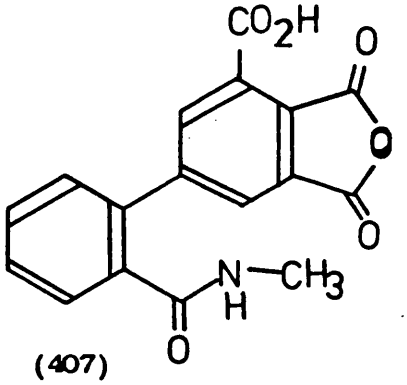

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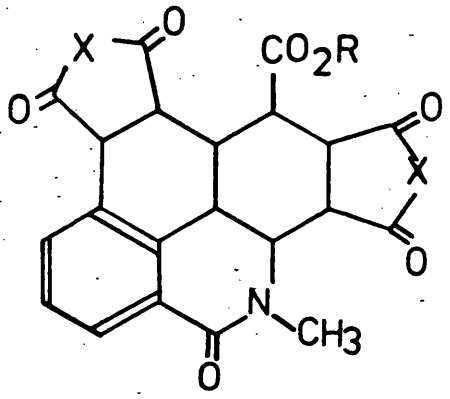
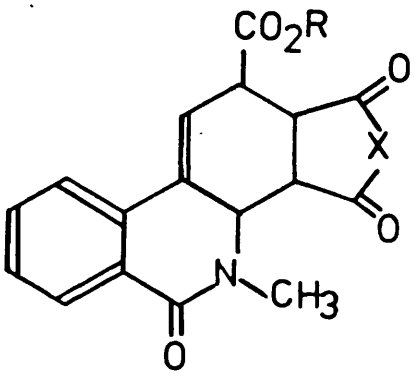




(408) R = CH_3 ; X = $\geq NCH_2CH_3$

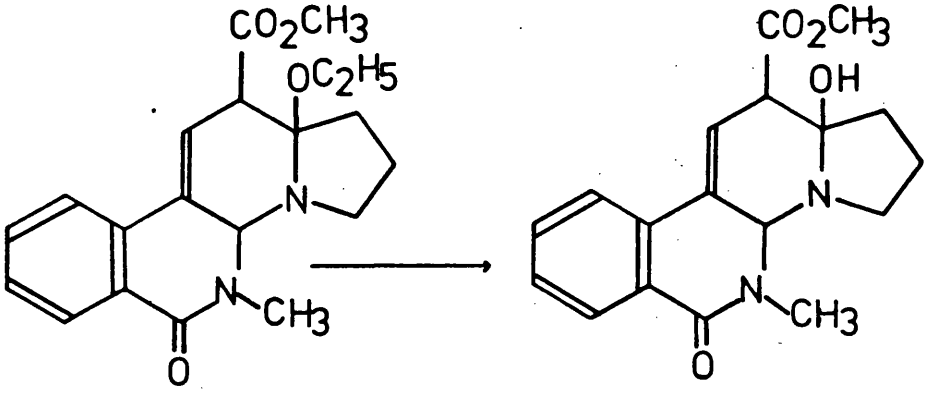
(412) R = C_2H_5 ; X = $\geq NC_6H_5$

(409) R = CH_3 ; X = $\geq N{\cdot}C_2H_5$

(410) R = C_2H_5 ; X = $\geq O$

(411) R = C_2H_5 ; X = $\geq CH_2$

(413) R = C_2H_5 ; X = $\geq N{\cdot}C_6H_5$



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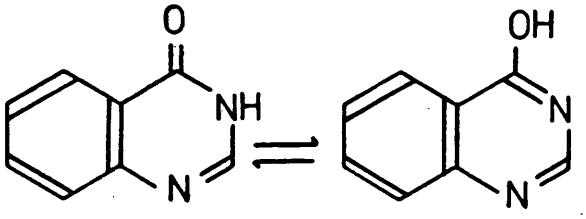

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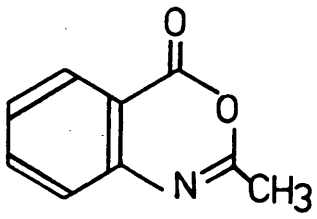

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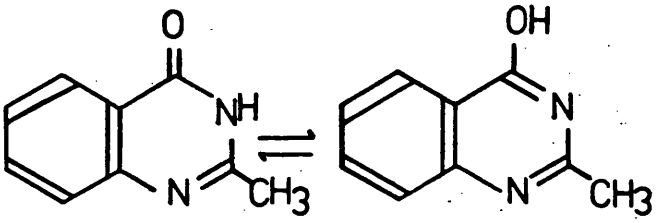

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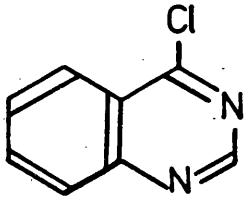

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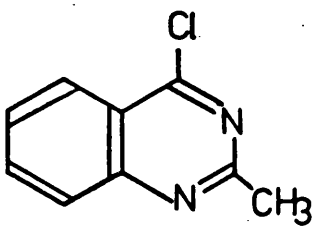

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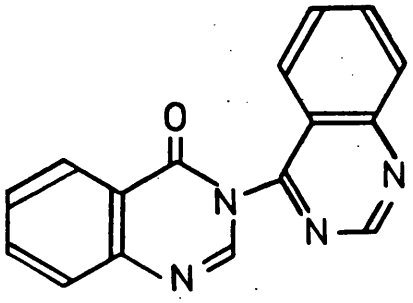

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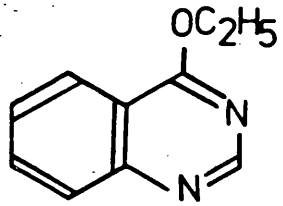

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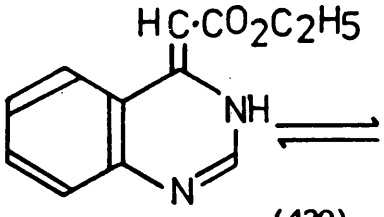

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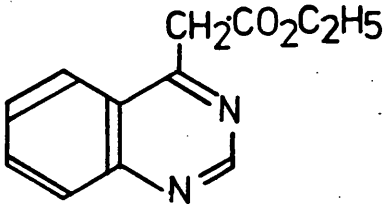

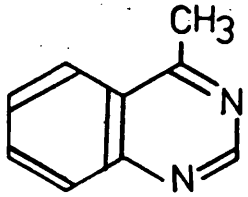

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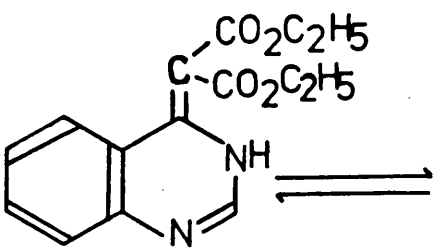

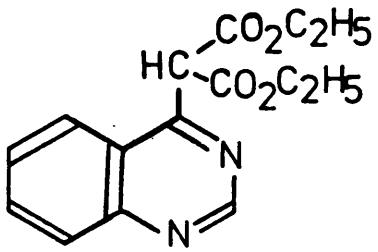

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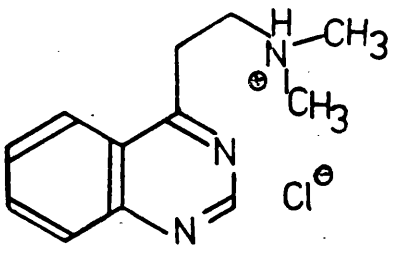

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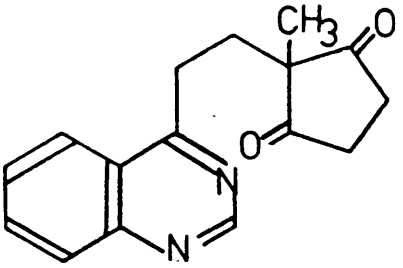

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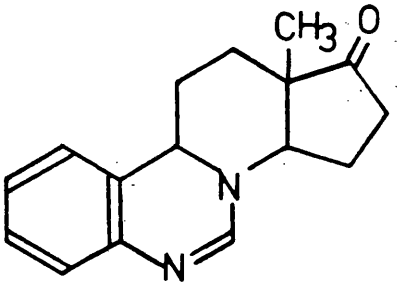

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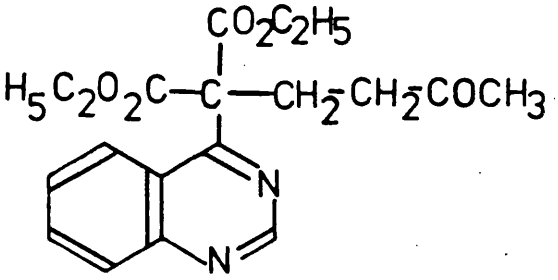

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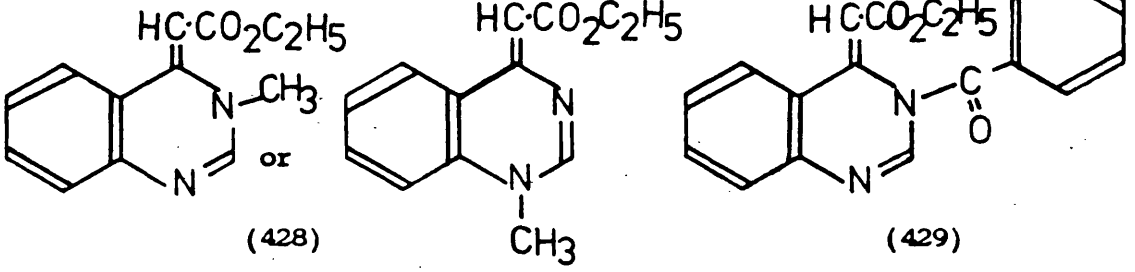

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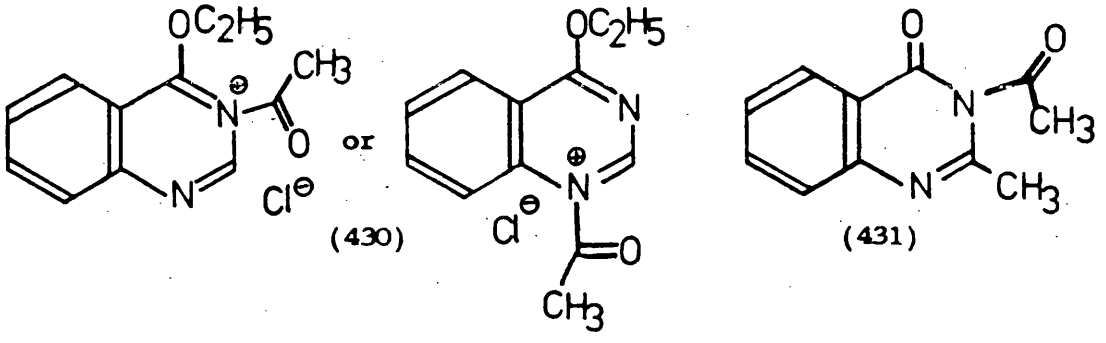
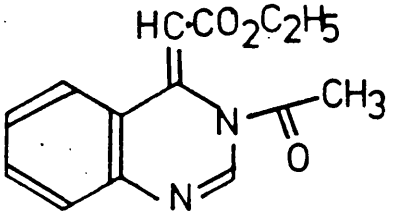


(430) (431)



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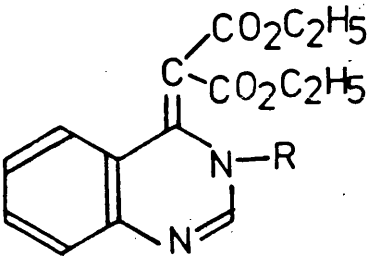
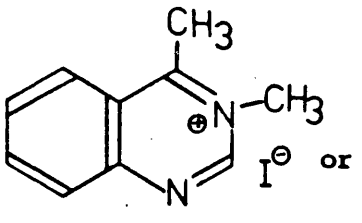


(433) R = CH_3

(434) R = $CO \cdot CH_3$

(435) R = $CO \cdot C_6H_5$



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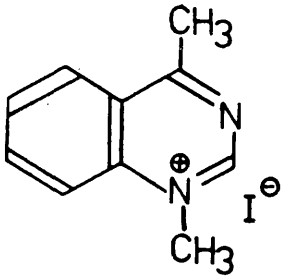

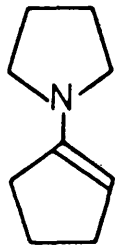

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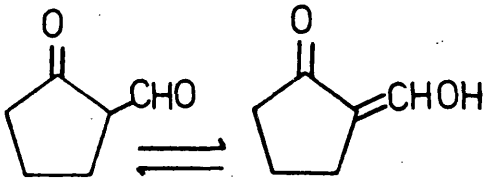

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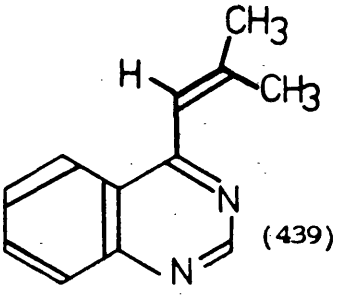

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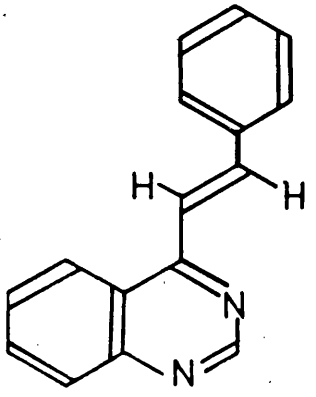

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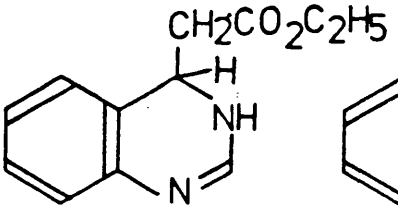

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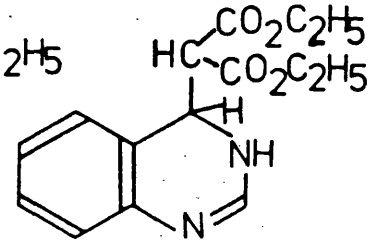

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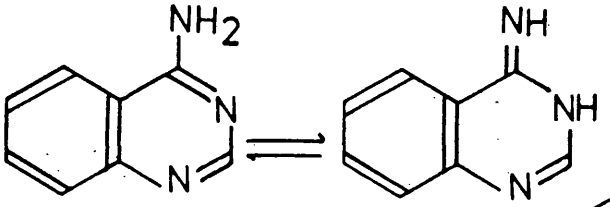

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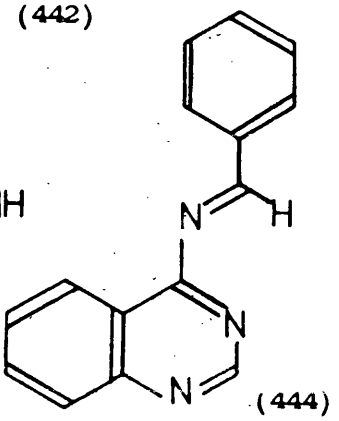

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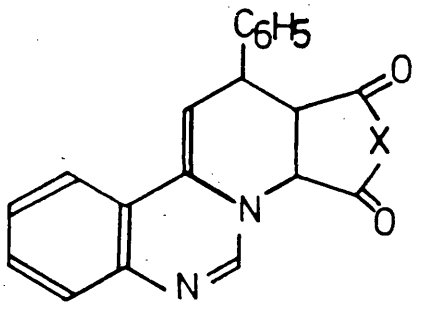
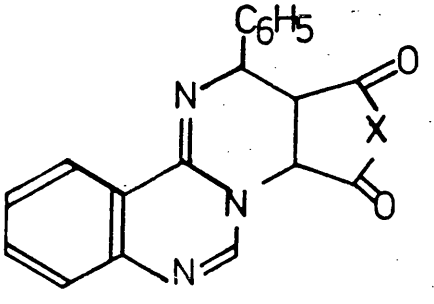


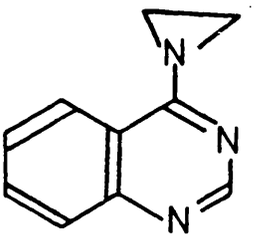
(445) X = >O

(446) X = >N·C$_6$H$_5$



(447) X = >O

(448) X = >N·C$_6$H$_5$



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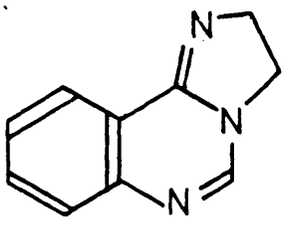
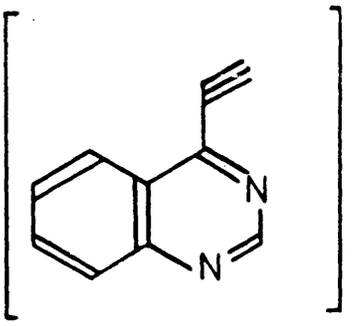


(450)



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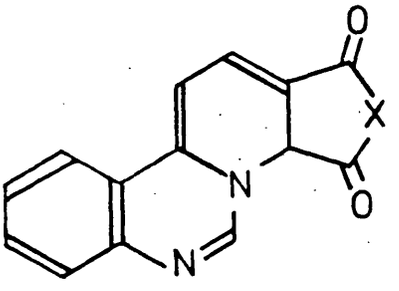

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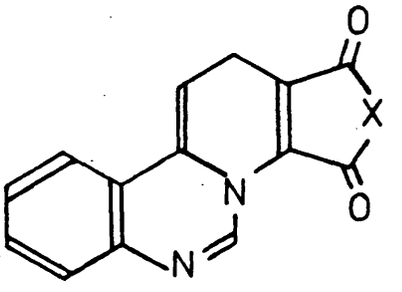
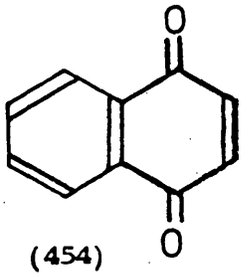


(452) X = >O

(453) X = >N·C_6H_5



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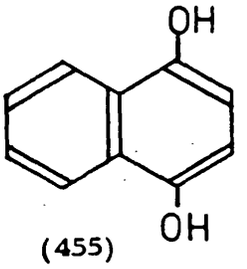

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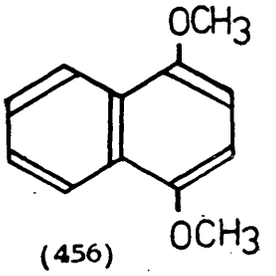

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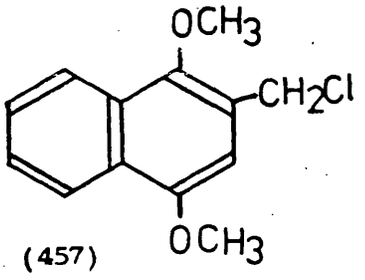

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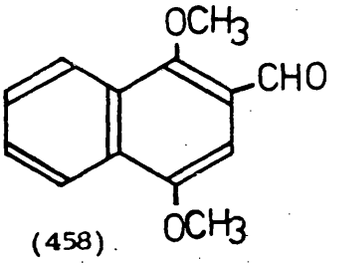

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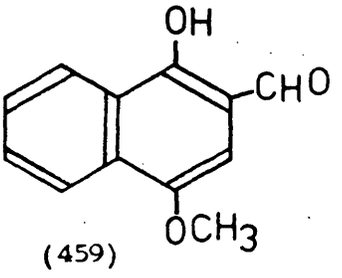

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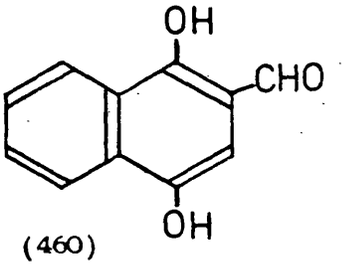
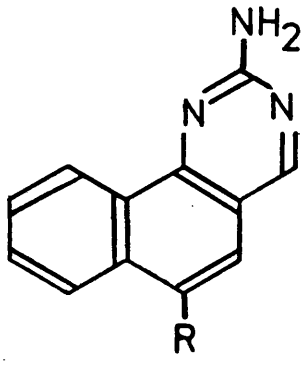
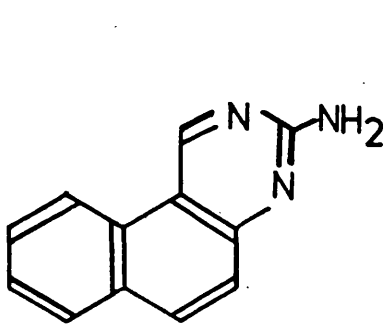


(460)



(461) R = OCH_3

(462) R = OH



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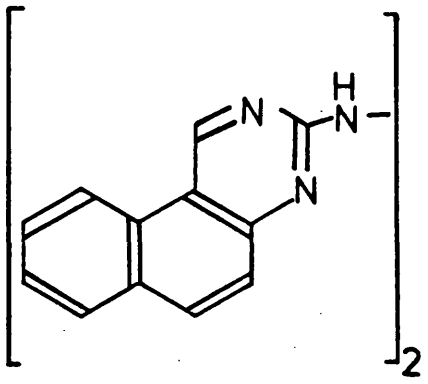
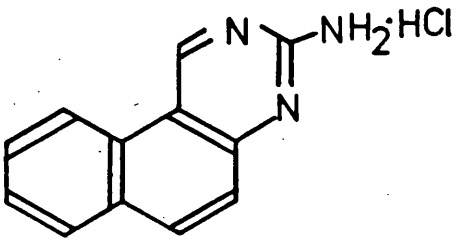
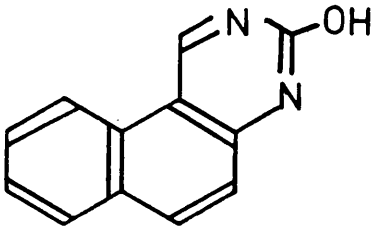


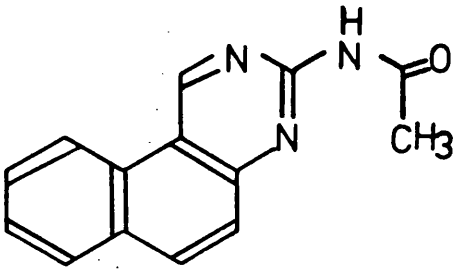
(464)



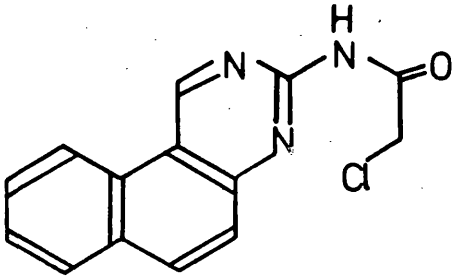
(465)



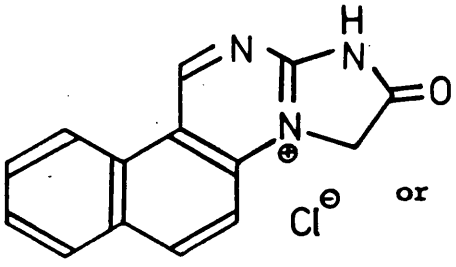
(466)



(467)

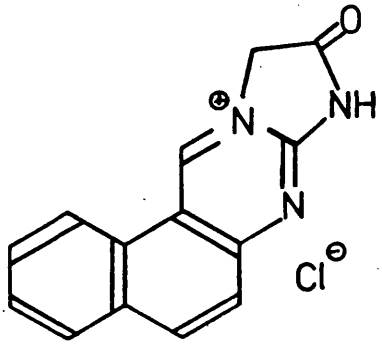


(468)



(A)

or



(B)

(469)

PLATE 1

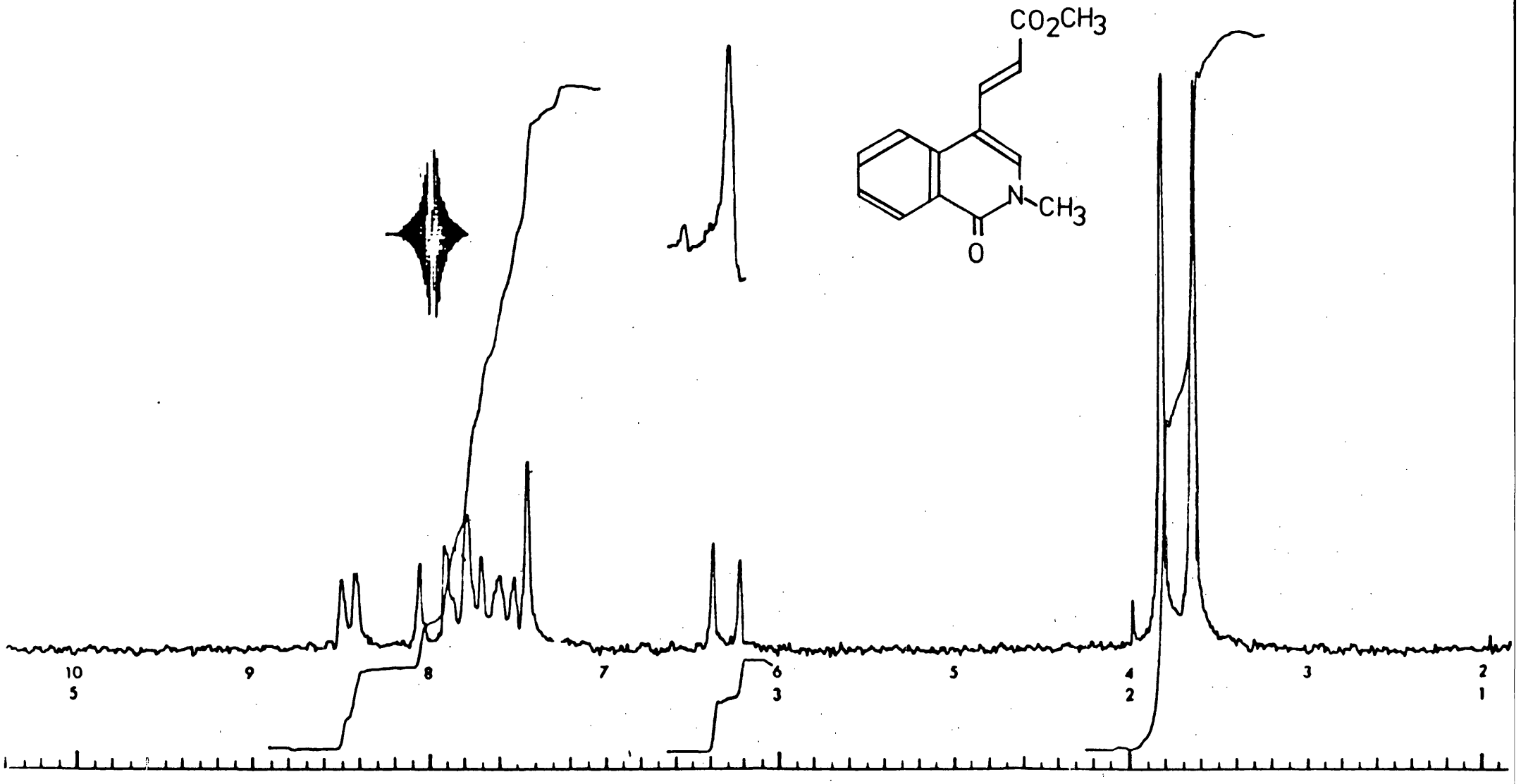


PLATE 2

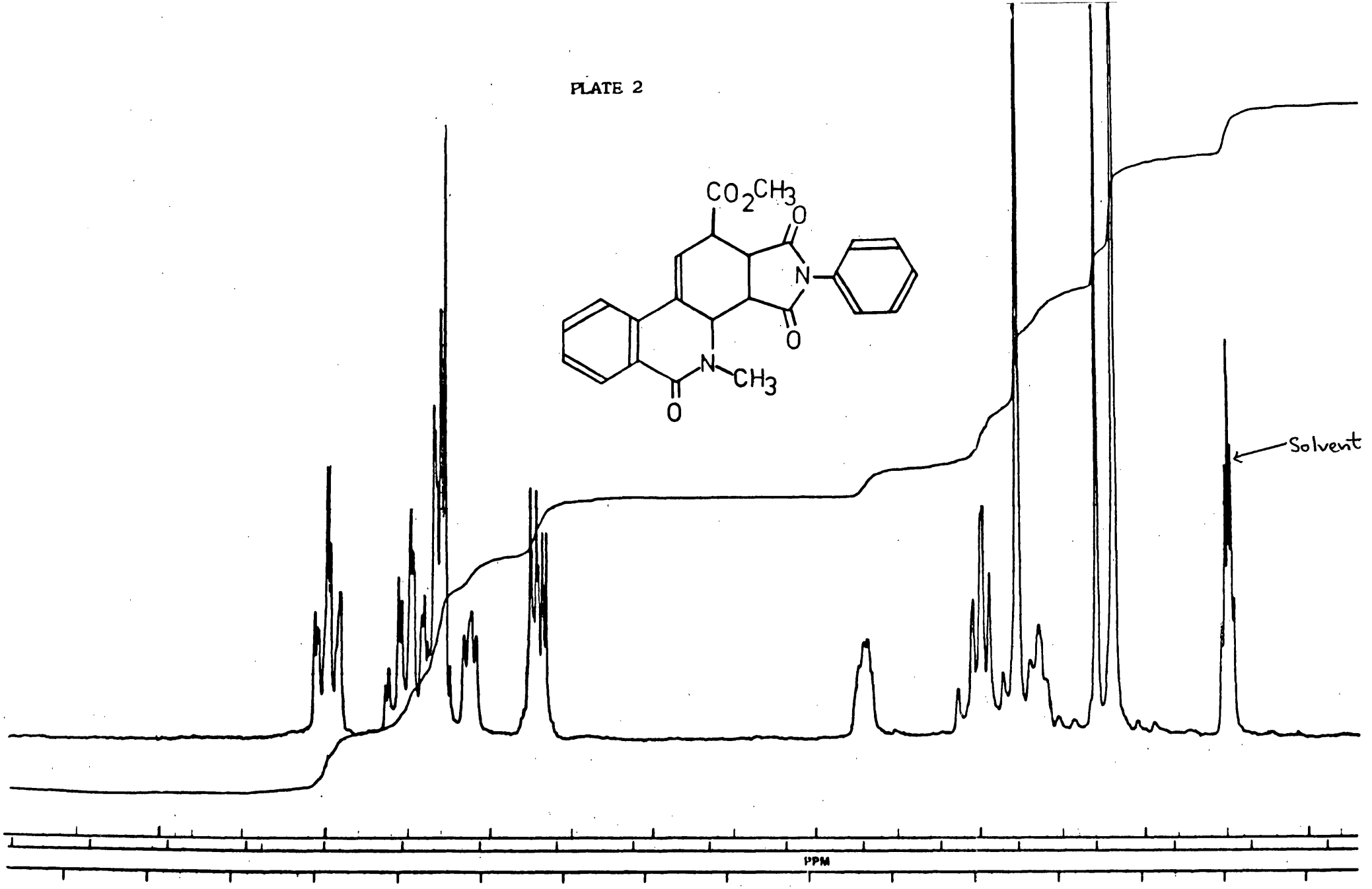


PLATE 3

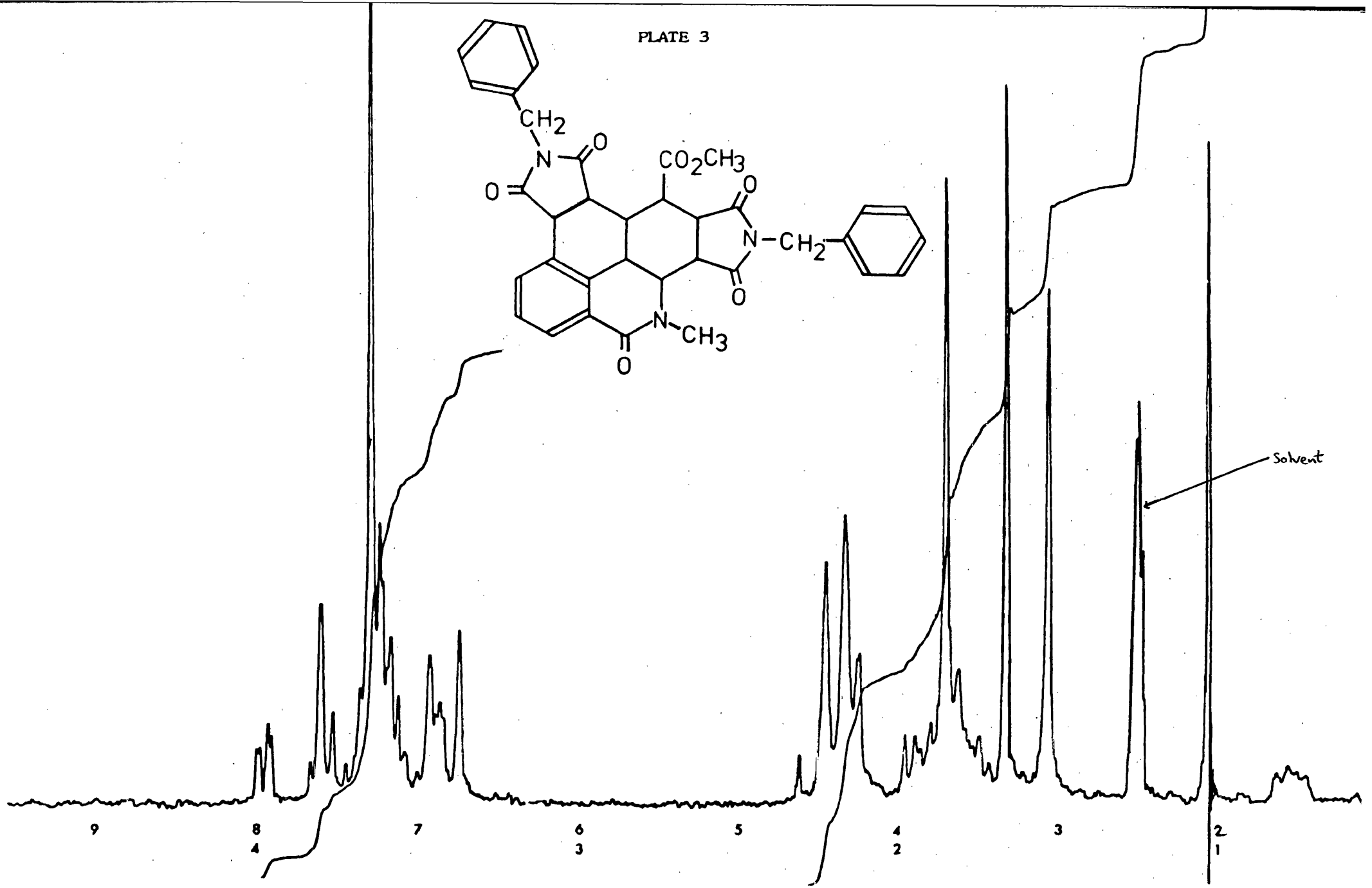


PLATE 4

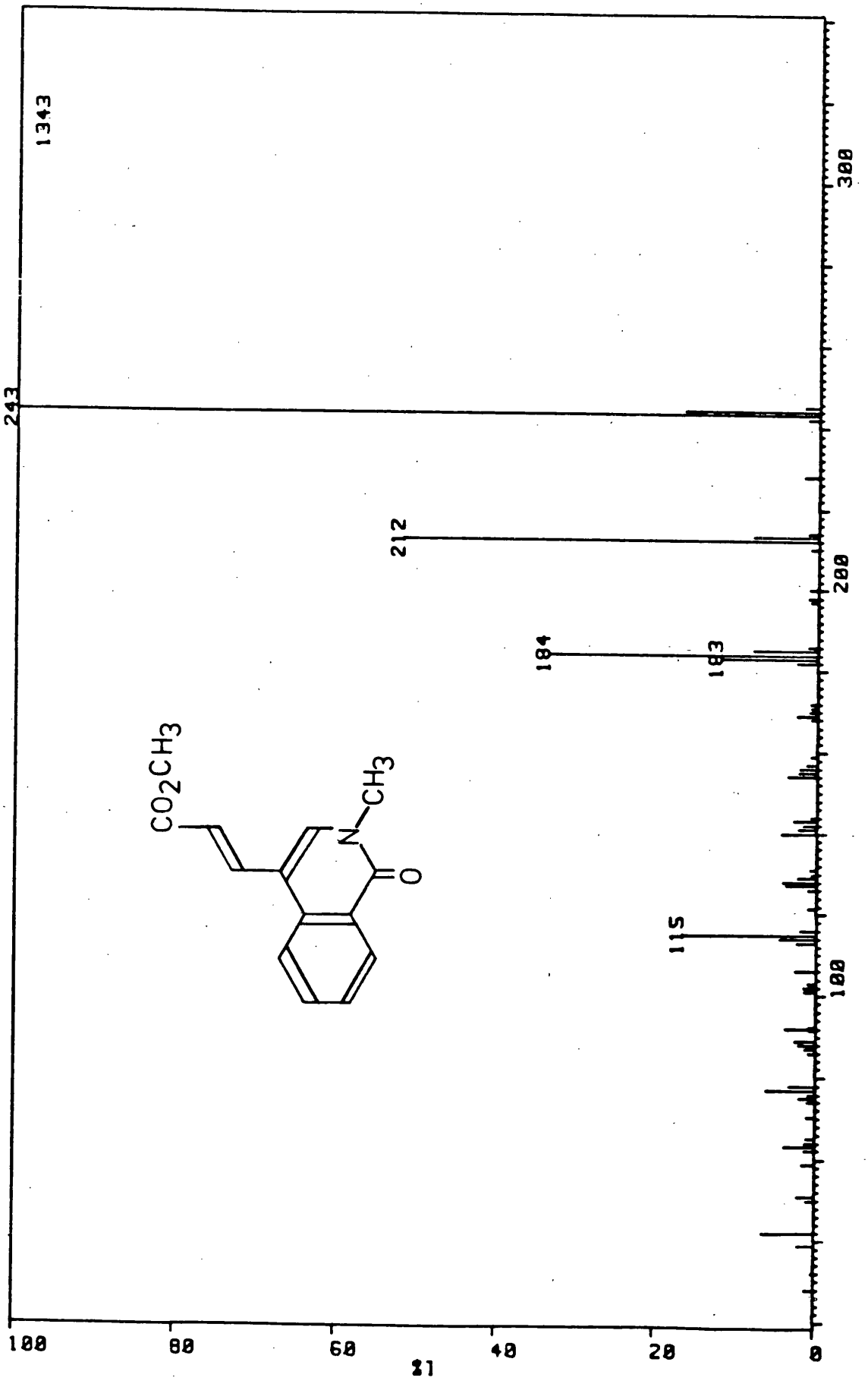
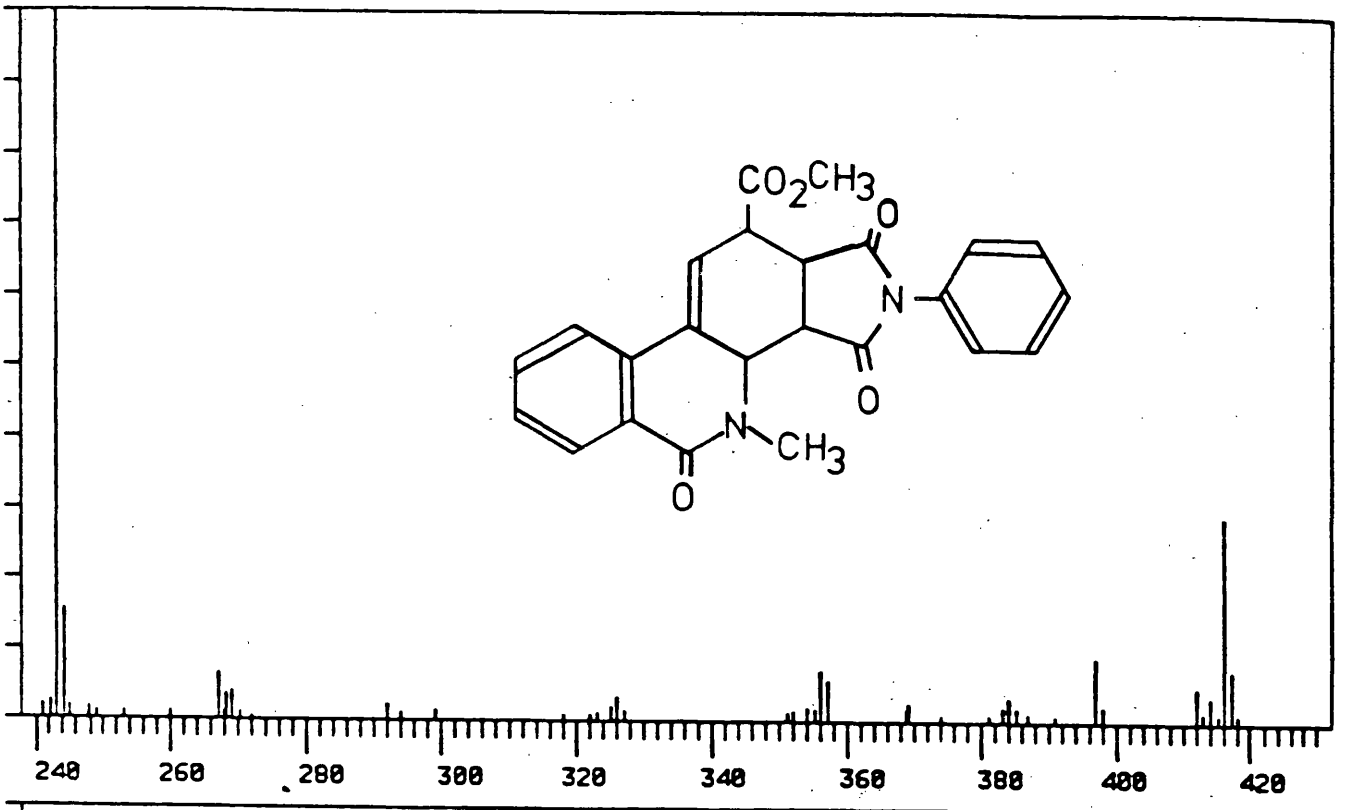

1343
243
212
184
183
115
300
200
100
0
100
80
60
40
20
0
%I
CO_2CH_3
CH_3
N
O

PLATE 5


CO2CH3
O
N
O
N
CH3
O
240
260
280
300
320
340
360
380
400
420

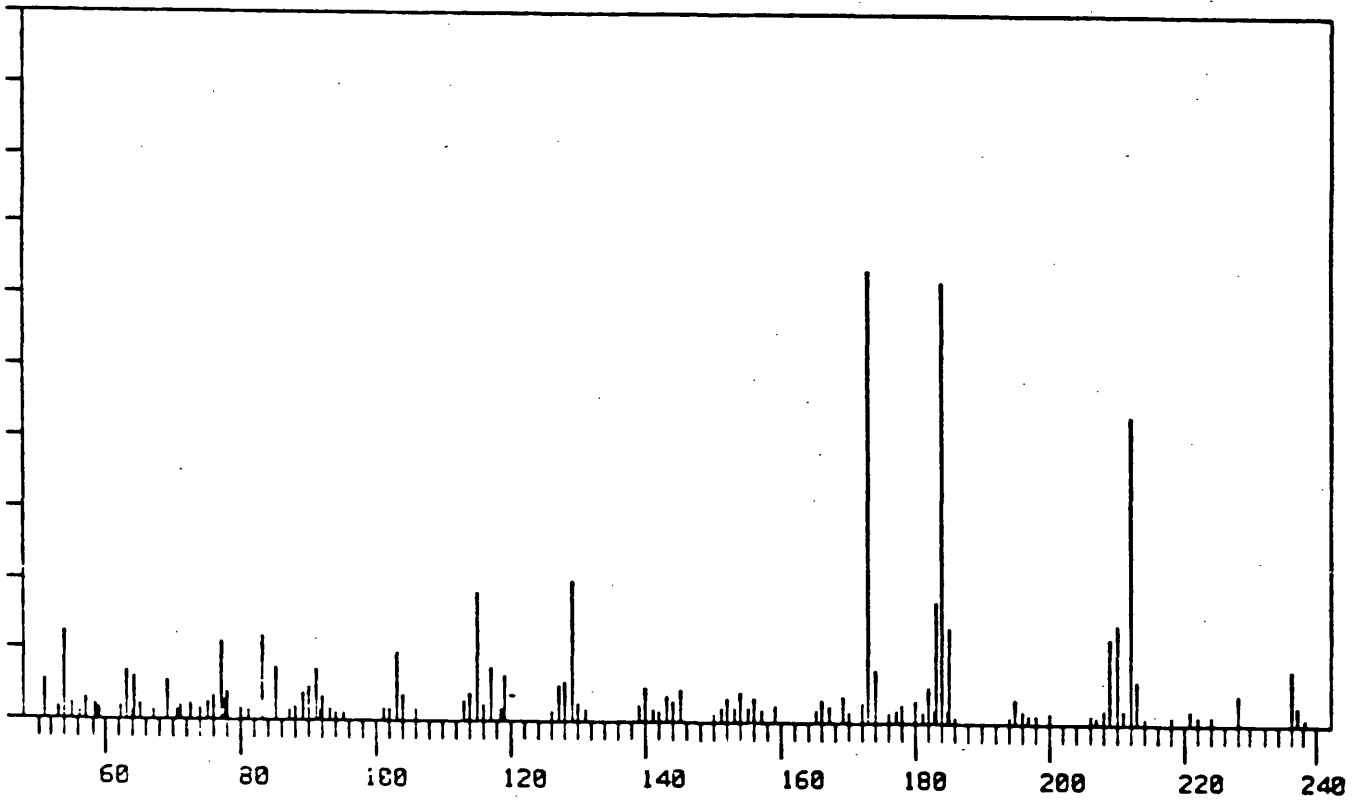
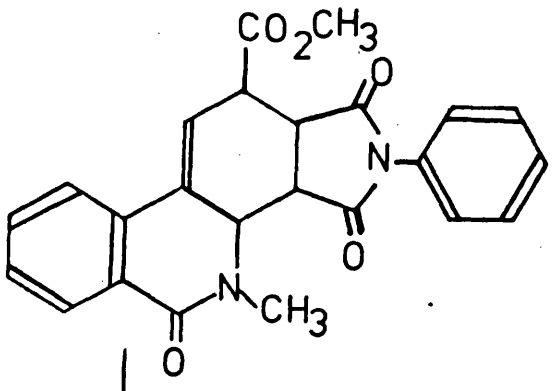

60
80
100
120
140
160
180
200
220
240

PLATE 6



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